

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	mirabegron
(Proposed) Trade Name	Myrbetriq
Therapeutic Class	Beta-3- adrenoceptor agonist
Applicant	Astellas Pharma Global Development, Inc.
Formulation(s)	Oral
Dosing Regimen	Once Daily
Indication(s)	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency
Intended Population(s)	Women and Men with Overactive Bladder

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 202-611 be **APPROVED** at this time.

1.2 Risk Benefit Assessment

A thorough and comprehensive review of NDA 202-611 was carried out. The NDA submission provided substantial evidence from adequate and well controlled (“pivotal”) studies that mirabegron 25 mg and 50 mg is safe and effective for the treatment of overactive bladder.

Efficacy data from three, Phase 3 studies (178-CL-046, -047, and -074) demonstrates that the primary efficacy objectives (reduction in daily incontinence episode and micturition frequency) were achieved in all three studies for mirabegron 50 mg once daily, as well as in Study 178-CL-074 for mirabegron 25 mg daily. While the primary efficacy endpoint data were comparable between mirabegron 25 mg and mirabegron 50 mg in Study 178-CL-74, a modest benefit of the 50 mg dose over the 25 mg dose was observed for several clinically meaningful secondary efficacy endpoints. In order to maximize the risk/benefit equation for mirabegron, this reviewer considers it reasonable and appropriate to initiate mirabegron therapy at 25 mg once daily, to provide a trial of the 25 mg dose, and to increase the dose to mirabegron 50 mg daily on an individual patient basis as needed, based on efficacy and tolerability of the 25 mg dose. The drug product labeling will recommend such dosage and administration.

Within the three pivotal studies (178-CL-046, 178-CL-047 and 178-CL-074) and the 52 week blinded active comparator safety study (178-CL-049), patient exposure to mirabegron was extensive:

- A total of 4368 subjects were exposed to mirabegron 25 mg, 50 mg or 100 mg in all OAB studies with a total exposure of 1281.7 patient years.
- A total of 2736 subjects were exposed to mirabegron 25 mg, 50 mg or 100 mg in the “pivotal”, Phase 3, 12-Week, OAB studies.
- A total of 1632 subjects were exposed to mirabegron 50 mg or 100 mg in the active-comparator long-term (1-year) study.
- A total of 1385 and 564 subjects were exposed to either mirabegron 50 mg or 100 mg for at least 6 months and one year in the active comparator long term study.

There were no deaths attributable to mirabegron in the development program. In regard to SAEs, there were no differences observed in incidences between total mirabegron and placebo. The only serious adverse event reported by more than 1 mirabegron patient and at a rate greater than placebo was atrial fibrillation (mirabegron 50 mg, 0.2%). Adverse events leading to study discontinuation were only modestly higher in incidence for the total mirabegron group (3.8%)

compared to placebo (3.3%), and the mirabegron incidence was lower than the incidence reported for the active comparator (4.4%). 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%]). For the mirabegron 50 mg dose, the most frequent adverse reactions leading to discontinuation in the Phase 3, 12-Week, OAB studies were hypertension (0.2%) and tachycardia (0.1%).

In the 12 week Phase 3 Population the most common TEAE (by PT) in the total mirabegron group were hypertension (mirabegron: 200/2736 [7.3%]; placebo: 105/1380 [7.6%]; tolterodine: 40/495 [8.1%]), nasopharyngitis (mirabegron: 94/2736 [3.4%]; placebo: 35/1380 [2.5%]; tolterodine: 14/495 [2.8%]) and UTI (mirabegron: 83/2736 [3.0%]; placebo: 25/1380 [1.8%]; tolterodine: 10/495 [2.0%]). For the mirabegron 25 mg and 50 mg doses, the commonly reported adverse reactions were hypertension, nasopharyngitis, UTI, constipation, fatigue, tachycardia, and abdominal pain. The only events reported by >2% of mirabegron patients was hypertension, nasopharyngitis and UTI. Few, if any, events of hypertension were of new-onset. Most were fluctuations in blood pressure on a background of baseline hypertension.

There were several safety issues that underwent rigorous analysis during this NDA review. They included the following:

- Mirabegron was associated with a modest increase in heart rate and blood pressure in Phase 3 studies. Mean increase in heart rate was 1 bpm for mirabegron 50 mg, and mean increase in systolic blood pressure was 1 mmHg for mirabegron 50 mg. In two Phase 1 studies, including the through QT study 178-CL-077, BP increases of approximately 3 mmHg were observed for mirabegron 50 mg, and the BP increase with mirabegron appeared to be dose-related. Heart rate increases were also larger in Phase 1 compared to Phase 3.
- In the long-term, active-controlled study 178-CL-077, the incidence of serious adverse events of neoplasms was higher in the mirabegron 100 mg group compared to the mirabegron 50 mg group and the active control group: serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with mirabegron 50 mg, mirabegron 100 mg and active control once daily, respectively. The reports were of a wide variety of commonly occurring neoplasms in mirabegron 100 mg subjects (prostate cancer, lung cancer, breast cancer, endometrial cancer, etc). No single neoplasm was reported by more than 2 patients. The meaning of this signal is unclear.
- Two significant clinical hepatic adverse events were reported in the NDA, both with possible concomitant allergic phenomena. Both of these cases had confounding factors. In one of these cases, Stevens-Johnson syndrome with reported, along with increased serum ALT, AST and bilirubin in a patient taking mirabegron 100 mg and an acetaminophen-containing herbal medication.

The risk benefit analysis is, in my opinion, satisfactory for NDA approval. The data provided in the Sponsor's submissions support adequate directions for use, including the data to describe a

safe and effective dose. The submissions do allow for labeling that will permit safe and effective use of mirabegron 25 mg and 50 mg daily for the treatment of OAB.

1.3 Recommendations for Postmarket Risk Management Activities

The Sponsor agreed to conduct two postmarketing studies to further assess the clinical significance of the blood pressure and neoplasm issues, respectively. The Sponsor has also agreed to conduct enhanced post-marketing surveillance for spontaneously reported hepatic adverse events. Extra attention and follow-up will be given to such events and enhanced attention will be paid to this area in the periodic adverse event reports (PADER) to the NDA.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The Sponsor agreed to conduct two post marketing studies as postmarketing requirements:

- The first study will be a claims-database centered cardiovascular outcomes study. An outline of this study was submitted in the Sponsor's presentation materials for the Advisory Committee Meeting. A more detailed protocol synopsis was submitted to the NDA and it outlines an assessment of major cardiovascular events in users of mirabegron versus non-users. The purpose of this study is to assess cardiovascular risks in patients using mirabegron in light the mirabegron induced modest increase in blood pressure.
- The second study will be an observational cohort study to assess the potential mirabegron-associated risk of new malignancies. This study will further assess the discordant finding in Study 178-CL-049 for neoplasm in the mirabegron 100 mg group compared to the mirabegron 50 mg or active control groups. A protocol synopsis for this study has been submitted and is under review. The Sponsor will likely need to access a number of databases that capture the occurrence of new malignancies, perhaps including international databases. If such a study is attempted and proves difficult logistically, a prospective observational cohort may be required.

At the current time, neither the blood pressure nor neoplasm issue precludes approval, especially in light of the low starting dose (mirabegron 25 mg once daily), and the theoretical risk of neoplasms at 2-4 times the marketed dose..

2 Introduction and Regulatory Background

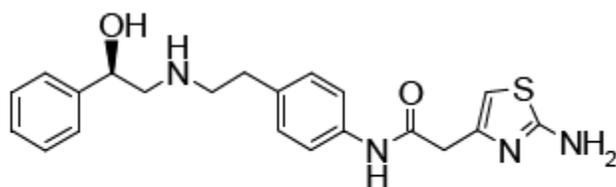
2.1 Product Information

Mirabegron is to be marketed under the trade name of Myrbetriq. Mirabegron is beta-3 adrenoceptor (AR) agonist and is a new molecular entity (NME). The proposed indication for use is for the treatment of overactive bladder (OAB) with symptoms or urge urinary

incontinence, urgency, and urinary frequency in adult men and women. The to-be marketed dose regimen will be a starting dose of 25 mg once daily with increase in dose to 50 mg once daily in those patients who do not achieve satisfactory response. The 25 mg dose once daily will also be available for use in patients with moderate hepatic or severe renal impairment.

The chemical name of mirabegron is 2-(2-aminothiazol-4-yl)-N-[4(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide having an empirical formula of C₂₁H₂₄N₄O₂S and a molecular weight of 396.51.

Figure 1: Mirabegron Molecule



Mirabegron

Source: Figure 21, Clinical Overview, page 15.

Since the immediate release formulations of mirabegron 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 tablet using Astellas' oral controlled absorption system (OCAS) was developed. OCAS modified release formulation is also referred to as extended-release or prolonged-release. Alcohol is unlikely to accelerate mirabegron dissolution and release from the OCAS formulation in the Sponsor's opinion. Mirabegron OCAS tablets exhibited a decrease in plasma exposure with food that was dependent on meal composition (low-fat versus high-fat). Coadministration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC_{inf} by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC_{inf} by 75% and 51%, respectively.

After oral administration of mirabegron in healthy volunteers, mean peak plasma concentrations were reached between 3 and 4.3 hours. Mirabegron is a substrate for the efflux transporter P-gp and the influx organic cation transporters. The absorption of mirabegron is dose-dependent, likely attributed to saturated efflux transporters in the intestine. 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. In-vitro erythrocyte concentrations of ¹⁴C-mirabegron were about 2-fold higher than in plasma, indicating that mirabegron distributes to erythrocytes.

Total body clearance (CL) of mirabegron from plasma is approximately 57 L/h. Blood clearance is estimated to be approximately 41 L/hr, which is about half the liver blood flow. Following an initial more rapid distribution phase, the $t_{1/2}$ of mirabegron is approximately 50 hours. The $t_{1/2}$ was independent of dose, route of administration and formulation, indicating no absorption-rate limitation in the PK of the OCAS tablet. The effective half-life is estimated to be about 19 hours (based on population PK analysis). 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.

Mirabegron is 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 (UGT), 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. None of the metabolites observed in plasma were pharmacologically active.

Age has no clinically relevant impact on mirabegron exposure. Mirabegron C_{max} and AUC_{tau} were approximately 40% to 50% higher, respectively, in females compared with males. The magnitude of the sex differences is attenuated with correction for body weight. Weight-normalized values for C_{max} and AUC_{tau} were approximately 20% to 30% higher in females compared to those in males. No dose adjustment based on sex is recommended by the Sponsor. There were no apparent differences in PK parameters among subjects of White, Black, Asian or other racial origin. In addition, race was not found to influence any of the PK parameters in the population PK analysis of phase 2 and 3 data. Plasma exposure in Japanese healthy subjects was higher than in Western subjects, which was largely related to differences in body weight. Dose adjustment based on race is not necessary. 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 and 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 subject with a body weight of 30 kg and approximately 17% lower in a subject 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_{tau} , respectively).

Genetic polymorphism for the CYP2D6 isozyme has no clinically relevant impact on mirabegron exposure. Following a single 160 mg dose of mirabegron administered as the IR formulation, mean C_{max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC_{tau} was 8% and 12% higher, respectively, in CYP2D6 poor metabolizers

compared to extensive metabolizers, and mean C_{\max} values were similar between the two phenotypes.

Volunteers with renal impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and weight. Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m² as estimated using the Modification of Diet in Renal Disease [MDRD] 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 m²), 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 m²), mean C_{\max} and AUC_{inf} values were 92% and 118% higher, respectively. Although these increases in mirabegron C_{\max} and AUC_{inf} are less than achieved with doubling of the dose, a reduction of the dose to 25 mg once daily in patients with severe renal impairment is recommended. No adjustment of the dose is required in patients with mild to moderate renal impairment according to the Sponsor.

Volunteers with hepatic impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and body mass index (BMI). 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. Although the increase in mirabegron AUC_{inf} is less than achieved with doubling of the dose, a reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment is recommended. The Sponsor recommends no adjustment of the dose in patients with mild 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 by the Sponsor.

2.2 Tables of Currently Available Treatments for Proposed Indications

OAB can be managed by various treatment modalities, including bladder and behavioral training, biofeedback, electrical stimulation, surgery or pharmacotherapy. The pharmacotherapeutic treatment options indicated for OAB are muscarinic receptor antagonists, such as solifenacin, oxybutynin, trospium, darifenacin, tolterodine and fesoterodine.

Table 1: Currently Available Treatments for Overactive Bladder

Treatment Modality	Regimen	Advantages	Disadvantages/AEs
Behavioral Therapy	Fluid restriction, bladder training, double voiding, scheduled toilet trips	Low cost and low risk	Usually not effective as stand alone therapy
Pelvic Floor Therapy	Kegel’s maneuver with or without biofeedback, Can require instruction with multiple visits	Low risk, may be done along with behavioral therapy	Usually not effective as stand alone therapy
Antimuscarinic Agents	Daily dose of agents either by patch, topical gel application or oral dosing	Mainstay of current OAB therapy. Modest efficacy.	Chronic use A/Es: dry mouth, constipation, blurred vision: glaucoma contraindication: 27% of OAB patients fail on medication: drug costs: Urinary retention
Neuromodulation	Surgical implantation (sacral nerves) of an electrical stimulator	Used in refractory patients	Surgical procedure, device and lead failure, decreased efficacy over time in some patients
Peripheral Nerve Stimulation	Regularly scheduled visits with placement of external electrode to stimulate either the posterior tibial or pudendal nerve by PTNS	This is a secondary therapy. Can be considered prior to neuromodulation. Less invasive than neuromodulation.	No systemic AEs. Local needle site AEs: discomfort, bleeding, and tingling in leg (posterior tibial site). No substantial evidence of efficacy
Botulinum Toxin	Single intravesical injection session using approximately 200 units of botulinum toxin. May need to repeat at 6+ months	Can be used in lieu of neuromodulation. Treatment effect may persist for 6+ mos.	Not an FDA approved therapy for regular OAB. Death and paralysis possible though unlikely. Allergic reactions. Increase of PVR, retention, possible need for intermittent

			catheterization, infection,
Bladder Augmentation	Surgical procedure using intestinal segments to increase bladder capacity	Usually and infrequently done when all other options are exhausted	Risks and complications of abdominal surgery. Bladder pain and urgency may not be eliminated. Patients may require chronic intermittent catheterization

Sources: Journal of Urology 2010, Volume 183(4) pages 1282-1283, 1432-1437, 1438-1443: Mayo Clinic Health Letter, accessed on-line, 10 October 2011, Overactive Bladder: Treatment and Drugs.

2.3 Availability of Proposed Active Ingredient in the United States

Mirabegron is a new molecular entity. It was approved for marketing in Japan 1 July 2011.

2.4 Important Safety Issues With Consideration to Related Drugs

While the data are limited on the effects of beta-3-AR agonists, Study-CL-053 suggests that mirabegron may not be a selective beta-3-AR agonist. The important safety issues include cardiovascular effects (increase in heart rate and increase in blood pressure), urinary tract events (including urinary tract infections and rare cases of urolithiasis), delayed hypersensitivity reactions, occurrence of a variety of neoplasms in the long-term study, and two cases of hepatotoxicity in association with hypersensitivity. The reader is referred to Section 6, Review of Efficacy and Section 7, Review of Safety for further discussion of these safety issues.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Mirabegron is an agonist for human beta 3-adrenoceptor (beta 3-AR) developed by Astellas Pharma. The Sponsor seeks an indication for the treatment of OAB. Mirabegron is a new chemical entity, first-in-class compound with a distinct mechanism of action compared with the current standard of care, primarily antimuscarinics, as pharmacotherapy for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency. The proposed dose is 50 mg of mirabegron once daily with or without food. In patients with severe renal impairment or with moderate hepatic impairment the recommended dose of mirabegron is 25 mg orally with or without food. Mirabegron has been approved for marketing in Japan (July 2011).

The Sponsor opened IND 69,416 on May 9, 2006. An End-of-Phase 2 meeting was held with the Sponsor on November 14, 2007. At that time, the planned Phase 3 studies were discussed. Several safety issues were discussed, including isolated cases of elevations in liver function tests, and increases in blood pressure in some individuals in Phase 2 studies. The Division requested that blood pressure and liver function be monitored in the Phase 3 studies. In January 2008, following submission of phase 3 study protocols for special protocol assessment (SPA), the Division provided the Sponsor with Phase 3 protocol review comments which recommended that a 25 mg dose of mirabegron be evaluated (b) (4)

In the spring and summer of 2010, the Division of Reproductive and Urologic Products had three meetings to discuss mirabegron and possible glaucoma cases reported during the mirabegron development program. After review of additional analysis and data submitted by the Sponsor, the concern persisted that mirabegron could increase intra-ocular pressure (IOP). The Sponsor proposed a protocol to evaluate the effect of mirabegron on IOP. The proposal was reviewed by the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products. Protocol 178-CL-081 was submitted incorporating FDA recommendations on 22 September 2010.

At the Pre-NDA meeting held on November 2, 2010, the Phase 3 study results were discussed. As part of the planned NDA, the Sponsor proposed to systematically review several adverse events of interest to which the Division agreed. These adverse events of interest were:

- Cardiovascular events including increases in blood pressure, QT prolongation or its sequelae, and cardiac arrhythmias;
- Urinary tract events, including urinary retention/acute urinary retention, urinary tract infection, and urolithiasis;
- Hypersensitivity reactions;
- Lowering of the blood pressure, syncope, and hypotension;
- Seizures;
- Increases in serum liver function tests;
- Cases reported as “glaucoma” or “increased intraocular pressure”; and
- Single reports of a variety of neoplasms

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of acceptable quality and organization. No concerns have been raised about the integrity of the processes that were used by Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor appears to have been compliant with good clinical practices.

3.3 Financial Disclosures

Form FDA 3454, dated July 26, 2011, and signed by Stephen Knowles, Vice President, Finance and Procurement, Astellas Pharma Global Development, Inc., was submitted. Financial disclosure documents (Form 3455) were submitted for clinical investigator [REDACTED] (b) (6), an investigator in the 178-CL-047 and 178-CL-049 clinical studies, indicated receiving significant payments of other sorts (as defined in 21 CFR 54.2(f)) from Astellas, as related to his national consulting role in regards to VESicare and honoraria. Since these significant payments of other sorts are related to another drug, this is not related to the research he conducted as an investigator in the mirabegron clinical studies.

A total of 189 investigators from 189 sites in Study 178-CL-046, 128 investigators from 128 sites in Study 178-CL-047, and 147 investigators from 147 sites in Study 178-CL-074 were enrolled. Study 178-CL-049 was conducted at 306 sites. Only one investigator had disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.2(a)], proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product [21 CFR 54.2(b)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.2(f)]. There was no disclosed missing financial disclosure information for investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

There were no significant efficacy or safety issues from the CMC perspective.

4.2 Clinical Microbiology

There are no clinical microbiology issues for this application.

4.3 Preclinical Pharmacology/Toxicology

The product is designated a Pregnancy category C, wherein use is recommended in pregnancy only where the potential benefit would outweigh the risks to patient and fetus. Reproductive toxicology studies showed some fetal effects but only at substantial multiples of exposure (e.g., 22-fold and 36-fold exposures at the maximum recommended human dose). Mirabegron was neither genotoxic nor carcinogenic. There were no significant efficacy or safety findings from the PharmTox perspective.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Mirabegron is an agonist for human beta 3 adrenoceptor. Pre-clinical studies have shown that activation of beta-AR in the bladder trigone facilitates urine storage through flattening and lengthening of the bladder base. The beta 3-AR subtype is dominant in the human detrusor muscle. In animal studies functional evidence was generated with the beta 3-AR agonists showing that activation of beta 3-ARs promoted urine storage in rats by increase of bladder capacity. In addition, it was shown that activation of beta 3-ARs increased urinary bladder capacity in models for induced bladder hyperactivity conditions in rats.

4.4.2 Pharmacodynamics

Cardiovascular:

A dedicated study to explore the effects and possible mechanisms of mirabegron on cardiac and vascular functioning in young healthy male adults suggests that beta-1 ARs may be involved in the cardiovascular responses observed at a high suprathereapeutic dose of 200 mg mirabegron (Study 178-CL-053). These changes resulting from a suprathereapeutic dose of mirabegron were attenuated by coadministration of a nonselective beta adrenoceptor antagonist, propranolol, as well as a selective beta-1 antagonist, bisoprolol.

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 nor at the suprathereapeutic 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. At both doses, the upper bound of the 1-sided 95% CI of corrected QT interval (QTc) interval did not exceed 10 msec at any time.

Vital Signs: Mirabegron was observed to increase both heart rate and blood pressure modestly, with larger increases observed in healthy volunteers in Phase 1 studies compared to increases observed in Phase 3 studies in OAB patients. In both healthy volunteers and OAB patients, a greater effect on heart rate and systolic blood pressure (SBP) as a function of mirabegron

exposure was observed in younger compared with older subjects, consistent with reported effects of beta 1-AR stimulation (Module 5.3.5.3 Cardiovascular Research Report). Gender had no effect on the exposure-response relationship for heart rate and SBP. Any observed gender differences in heart rate were substantially accounted for by the approximately 40% higher AUC in females compared with males, largely accounted for by smaller body weight in females (Module 5.3.5.3 Cardiovascular Research Report).

According to the Cardiovascular Research Report, in Phase 1 studies, mirabegron increased heart rate on electrocardiogram (ECG) in a dose dependent manner across the 50 mg to 200 mg dose range examined. The maximum observed mean difference from placebo in heart rate in Phase 1 studies in normal volunteers was 6.7 beats per minute (bpm) at mirabegron 50 mg. Mirabegron showed variable effects on systolic BP, with approximately 3 mm Hg mean increases observed in healthy volunteers in two Phase 1 studies, and even smaller mean increases (0.5 – 1 mm Hg) observed in OAB subjects in Phase 3. In OAB patients (mean age of 59 years) across three 12-week phase 3 double-blind placebo controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in SBP/DBP was observed. Changes in pulse rate and blood pressure were reversible upon discontinuation of treatment.

Intraocular Pressure: The effect of mirabegron on intraocular pressure (IOP) was formally examined in a pharmacodynamic (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, based on the non-inferiority limit of 1.5 mm Hg. The upper bound of the two-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. IOP data from day 10 were concordant with day 56. No subject discontinued the study due to an increased IOP. Clinically significant increases from baseline IOP measurements occurred rarely and only in placebo-treated patients.

4.4.3 Pharmacokinetics

The discussion below is to facilitate the clinical understanding of the pharmacokinetics of mirabegron and is in brief, a summary of the Sponsor's findings:

Since the immediate release formulations of mirabegron 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 tablet using Astellas' OCAS was developed. OCAS modified release formulation is also referred to as extended-release or prolonged-release.

After oral administration of mirabegron in healthy volunteers, mean peak plasma concentrations were reached between 3 and 4.3 hours. Mirabegron is a substrate for the efflux transporter P-gp and the influx organic cation transporters. The absorption of mirabegron is dose-dependent,

likely attributed to saturated efflux transporters in the intestine. 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. In-vitro erythrocyte concentrations of ¹⁴C-mirabegron were about 2-fold higher than in plasma, indicating that mirabegron distributes to erythrocytes.

Total body clearance (CL) of mirabegron from plasma is approximately 57 L/h. Blood clearance is estimated to be approximately 41 L/hr, which is about half the liver blood flow. Following an initial more rapid distribution phase, the $t_{1/2}$ of mirabegron is approximately 50 hours. The $t_{1/2}$ was independent of dose, route of administration and formulation, indicating no absorption-rate limitation in the PK of the OCAS tablet. The effective half-life is estimated to be about 19 hours (based on population PK analysis). 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.

Mirabegron is 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 (UGT), 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. None of the metabolites observed in plasma were pharmacologically active.

Genetic polymorphism for the CYP2D6 isozyme has no clinically relevant impact on mirabegron exposure. Following a single 160 mg dose of mirabegron administered as the IR formulation, mean C_{max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC_{tau} was 8% and 12% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers, and mean C_{max} values were similar between the two phenotypes.

5 Sources of Clinical Data

The Sponsor presents data in the following data analysis sets for safety:

- Global Phase 2 and 3: This population includes data from all patients who received at least 1 dose of mirabegron in any of the twelve (12) phase 2 and 3 studies conducted globally in Europe, Australia/New Zealand, South Africa, North America and Japan. This population includes patients who have received IR or OCAS formulations of mirabegron and patients with OAB, LUTS/BOO, or type 2 diabetes.

Reviewer's Comment: This data set contains results from use of mirabegron for different indications. The dose form used in some of the studies differs from that used in the EU/NA pivotal trials. The demographic of the patient population may not be typical of the EU/NA pivotal trials. Some of the protocols for these clinical trials were not reviewed or approved by the FDA. Additionally, 2 long term safety studies are included in this analysis data set.

- Global OAB 12-week Phase 2 and 3: This population includes data from six, 12 week, double-blind, placebo-controlled, phase 2 and 3 studies conducted globally in Europe, Australia, North America, and Japan in patients with OAB. Three of the 6 studies also include an active comparator group (tolterodine ER 4 mg). Studies 178-CL-046, 178-CL-047 and 178-CL-074 are pivotal studies for this NDA submission. Studies 178-CL-044, 178-CL-045 and 178-CL-048 are not pivotal studies for this NDA submission.
- EU/NA OAB 12-week Phase 3: This population pools data from three, 12 week, double-blind, placebo-controlled, phase 3 studies conducted in Europe, Australia and North America in patients with OAB (Studies 178-CL-046, 178-CL-047 and 178-CL-074). Study 178-CL-046 includes an active comparator (tolterodine ER 4 mg).

Reviewer's Comment: This analysis group is the primary data set to be reviewed for this NDA. These phase 3 studies protocols were reviewed and approved by the Division of Reproductive and Urologic Products prior to implementation. This analysis set provides data for more rigorous assessment of particular events of interest including vital signs, ECGs, and TEAEs specifically designed per protocol such as hypertension. The efficacy endpoints are standardized.

- EU/NA Long-Term Controlled: This population consists only of Study 178-CL-049 which is a large (approximately 800 patients in each arm), 12-month, double-blind, phase 3 study with an active-controlled tolterodine 4 mg comparator arm conducted in Europe, Australia/New Zealand, South Africa, Canada and the United States.

Reviewer's Comment: This is a large study and is the primary study to be used in evaluating long-term safety for US approval.

- Japan Long-term Uncontrolled: Population consists only of Study 178-CL-051, a 12-month, open-label, phase 3, dose-escalation study with starting dose of 50 mg mirabegron and potential increase to mirabegron 100 mg. Total patients exposed to mirabegron is 203.

Reviewer's Comment: The study includes only 153 subjects exposed exclusively to mirabegron for 52 weeks.

- Global Phase 1: The population includes data pooled from 26 phase 1 studies conducted globally in Europe, US and Japan. Studies 178-CL-080 (cardiovascular interaction

between mirabegron and tamsulosin), 178-CL-077 (TQT study), and 178-CL-081 (the effects of mirabegron on intraocular pressure) are not pooled with the other phase 1 studies.

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Clinical Studies with Mirabegron Included in Submission

Study Identifier	Study Objective	Design and Control Type	Test Product Dose Regimen Administration Route	Subject Number and Type	Duration of Treatment
Efficacy and Safety Studies					
178-CL-044 In 14 European Countries	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging	Treatment groups: placebo, mirabegron 25, 50, 100 or 200 mg, or tolterodine SR 4 mg or matching placebo po; once daily fed (after breakfast)	928 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-045 In Japan	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2, randomized, double-blind, placebo-controlled, parallel group	mirabegron 25, 50, or 100 mg qd or matching placebo tablet po; once daily fed (after breakfast)	842 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period

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178-CL-046 in Europe and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg, or matching placebo po; once daily with or without food	1987 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-047 in Canada, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg or matching placebo po; once daily with or without food	1329 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-048 in Japan	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo- and active-controlled	Treatment groups: placebo, mirabegron 50 mg, or tolterodine SR 4 mg or matching placebo po; once daily with food (after breakfast)	1139 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double-blind treatment period

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178-CL-049	Long Term Safety	Phase 3, randomized, double-blind, active-controlled	Treatment Groups: Mirabegron 50 or 100 mg or tolterodine ER 4 mg	2452	12 month double-blind treatment period
178-CL-074 in Canada, Europe and United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg or matching placebo po; once daily with or without food	1306 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-008 in Europe	Efficacy, safety, tolerability, population PK; proof of concept	Phase 2a, randomized, double-blind, parallel group, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron IR 100 or 150 mg bid, or tolterodine MR 4 mg	262 Adults with OAB	2-week single-blind placebo run-in followed by 4-week double-blind treatment period

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<p>178-CL-060 in Canada and United States</p>	<p>PD, safety, tolerability, PK</p>	<p>Phase 2a, placebo controlled, dose titration study</p>	<p>placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast</p>	<p>200 men with LUTS and BOO</p>	<p>12-week DB treatment period</p>
<p>178-CL-003 in Poland</p>	<p>PD, safety, tolerability, PK</p>	<p>Phase 2a, placebo controlled, dose titration study</p>	<p>Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast</p>	<p>59 Adults with type 2 diabetes</p>	<p>4-week single-blind placebo run-in followed by 12-week double-blind treatment period: Mirabegron 60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks</p>
<p>178-CL-004 In Poland</p>	<p>PD, safety, tolerability, PK</p>	<p>Phase 2a, placebo controlled, dose titration study</p>	<p>Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets)</p>	<p>60 Adults with type 2 diabetes on metformin monotherapy (stable doses)</p>	<p>4-week single-blind placebo run-in followed by 12-week double blind treatment period: Mirabegron</p>

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			or matching placebo po; once daily after breakfast Metformin 500 and 850 mg tablets po; stable dose throughout treatment period		60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks
Biopharmaceutic Studies					
178-CL-033 in Netherlands	Absolute BA (iv vs OCAS tablet)	Phase 1, open label, randomized, 2-way crossover	Mirabegron OCAS 50 mg or 150 mg tablet po, 15 or 50 mg iv over 2 hours; fasted	12 Healthy Volunteers	Single Dose
178-CL-030 in Netherlands	PK, 3 OCAS formulations vs IR	Phase 1, open label, 3-way crossover	Mirabegron OCAS-F 200 mg qd (fed and fasted), OCAS-S 200 mg qd (fed and fasted), OCAS-M 200 mg qd (fed and fasted); tablet po Mirabegron IR 100 mg bid (fasted); tablet po	36 Healthy Volunteers	8 days each treatment (OCAS fasted, OCAS fed, IR fasted), washout of ≥ 7 -days between treatments
178-CL-041 in United States	Effect of food on PK of mirabegron	Phase 1, randomized open-label, 3-way crossover	Mirabegron OCAS 50 or 100 mg tablet po; single dose administered fasted, with high-fat breakfast or with low-fat breakfast	76 Healthy Volunteers	Single dose on day 1 of each of 3 periods; washout of ≥ 10 days between periods
178-CL-064 in Japan	Effect of food on PK of mirabegron	Phase 1 randomized, open label, 2-way crossover	Mirabegron OCAS 50 mg tablet po; single dose administered fasted or with	24 Health Male Volunteers	Single dose on day 1 of each of 2 periods; washout

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			high-fat breakfast		of \geq 12 days between periods
178-CL-078 in Japan	Effect of food on PK of mirabegron	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	Mirabegron iv 7.5, 15 or 30 mg iv over 120 minutes and mirabegron OCAS 25, 50 mg or 100 mg tablet po (fast-release, target-release, slow-release and other target release); fasted	72 Healthy Volunteers	Single dose on day 1 of each of 3 periods; washout of \geq 12 days between treatments
178-CL-076 In United States	PK, iv and 3 OCAS formulations	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	91 Healthy Volunteers	Single dose on day 1 of each of 5 periods; washout of \geq 10 days between treatments
Human Pharmacokinetic Studies					
178-CL-001 in United Kingdom	PK, safety, tolerability, food effect	Part I Phase 1, placebo controlled, randomized, double-blind, dose escalation study	Placebo or mirabegron IR 0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, or 340 mg po; fasted	85 Healthy Male Volunteers	Single dose
		Part II Phase 1, open-label, randomized, 3-way crossover	Mirabegron IR 160 mg capsule (two 80 mg capsules) po; fed (with high-fat breakfast), semi-	12 Healthy Male Volunteers	Single dose, 7 day washout between doses

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			fed (30 min before high-fat breakfast), and fasted		
178-CL-002 in United Kingdom	PK, safety, tolerability, PD	Phase 1, placebo controlled, Double blind, randomized, dose-escalation study	Mirabegron IR 40, 80, 160, 240 mg capsule (20 and 80 mg capsules) po; once daily fasted Mirabegron IR 240 mg capsule (80 mg capsules) po; once daily fed (high-fat breakfast days 1 and 9; standard breakfast days 2-8)	40 Healthy Male Volunteers	Single dose on day 1 followed by once daily dosing for 7 days (days 3-9)
178-CL-007 in Netherlands	PK/mass balance	Phase 1, open-label study	C ¹⁴ -mirabegron 160 mg drinking solution; fasted	4 Healthy Male Volunteers	Single Dose
178-CL-031 in Netherlands	PK, safety, tolerability of OCAS-M formulation, explore PK in elderly and young	Phase 1, double blind, randomized, placebo-controlled, dose-escalating study	Mirabegron OCAS-M 50, 100, 200, 300 mg po; fasted on PK days, otherwise standard breakfast was served	96 healthy Volunteers	Single dose OCASM on day 2 followed by qd dosing for 10 days (days 5-14)
178-CL-066 in Japan	Dose proportionality of mirabegron	Phase 1 open-label, 3-period, dose escalation	Mirabegron OCAS 25, 50, and 100 mg tablet po; fasted	12 Healthy non-elderly male volunteers	Single dose on day 1 of each of 3 periods; washout of ≥ 12 days

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					between treatments
178-CL-034 in Japan: Single Dose	PK of mirabegron after single and repeated dosing	Phase 1, single blind, Placebo controlled, singled dose and repeated dose study	Single dose: Mirabegron OCAS 0 (placebo), 50, 100, 200, 300, or 400 mg; tablets po; fasted	40 Healthy Male Volunteers	Single Dose
178-CL-034 in Japan: Repeat Dose			Repeated dose: Mirabegron OCAS 0 (placebo), 100, or 200 mg tablet po; 30 min to 1 hour after breakfast	24 Healthy Male Volunteers	Single dose followed by 2-day washout, followed by 7 days
178-CL-072 in France	PK, safety, tolerability, age and gender effects	Phase 1, open-label, randomized, 2-way crossover	Mirabegron OCAS 25, 50 and 100 mg tablet po; 30 minutes after breakfast and dinner on day 1, 30 minutes after breakfast on days 2-5, fasted on days 6 and 7	75 Healthy Volunteers	Two 7-day treatment periods; morning and evening dose on day 1, single morning doses on days 2-7; washout of ≥ 14 days between treatments Treatment sequences included (Period 1 to Period 2): 25 to 50 mg; 50 to 25 mg, 25 to 100 mg;

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					100 to 25 mg; 50 to 100 mg; 100 to 50 mg
178-CL-038 in United States	PK, safety, tolerability, renal impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	33 Healthy Volunteers with mild to severe renal impairment	Single dose
178-CL-039 in Slovakia	PK, safety, tolerability, hepatic impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	32 Healthy Volunteers with mild or moderate hepatic impairment	Single dose
178-CL-005 In Netherlands	Part 1: PK in poor and extensive CYP2D6 metabolizers	Phase 1, open-label, 1-sequence, parallel study	Mirabegron IR 160 mg capsules (two 80 mg capsules) po; fasted	16 Healthy male volunteers (extensive and poor CYP2D6 metabolizers)	Single dose
	Part 2: DDI of mirabegron and metoprolol (CYP2D6 substrate)	Phase 1, open-label, cross-over	Mirabegron IR 160 mg capsules (two 80 mg capsules) once daily po; fasted metoprolol tartrate 100 mg tablet; fasted	12 Healthy male volunteers (extensive CYP2D6 Metabolizers)	7 days total single dose metoprolol on days 1 and 7, mirabegron on days 3-7
178-CL-006 in Netherlands	DDI of mirabegron and metformin	Phase 1, one sequence crossover	Mirabegron IR 160 mg tablets (one 100 mg tablet and two 30 mg tablets) po; once daily fasted Seq A: metformin 500 mg tablets; twice	32 Healthy Male Volunteers	Sequence A: mirabegron days 1-11 and mirabegron+metformin or placebo days 12-16 Sequence B:

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			daily on days 12-15, single morning dose on day 16, fasted (morning dose only) Seq B: metformin 500 mg tablets; twice daily on days 1-4 and 6-15, single morning dose on day 5 and 16, fasted (morning dose only)		metformin days 1-5 and metformin +mirabegron or placebo days 6-16
178-CL-058 in France	Effect of steady state mirabegron on PK of single dose desipramine	Phase 1, open-label, 1-sequence crossover study	Mirabegron OCAS 100 mg tablet po, only daily fasted; Desipramine 50 mg tablets (as two 25 mg tablets) po, fasted	28 Healthy volunteers	Period 1: desipramine 50 mg single dose on day 1; mirabegron 100 mg qd (day 5 to 23); desipramine 50 mg single dose in combination with mirabegron on day 18 (washout period 13 days) Period 2: desipramine 50 mg single dose on day 38
178-CL-	Effect of	Phase 1,	Mirabegron	30 Healthy	Dosed

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<p>068 in France</p>	<p>multiple doses of mirabegron on the PK of a COC</p>	<p>double-blind, 2-sequence crossover study</p>	<p>OCAS 100 mg or matching placebo tablet po; once daily fasted Combined oral contraceptive (COC) (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) tablet po; once daily fasted</p>	<p>Female Volunteers</p>	<p>according to menstrual cycle Period 1: COC qd day 1 to day 21; stop for 7 days; start mirabegron 100 mg or matching placebo qd day 12 for 10 days (washout period 19 days) Period 2: COC qd day 1 to day 21; start mirabegron 100 mg or matching placebo qd (opposite of period 1) day 12 for 10 days</p>
<p>178-CL-059 in France</p>	<p>Effect of steady state mirabegron on PK of single dose digoxin</p>	<p>Phase 1, open-label, 1-sequence crossover study</p>	<p>Mirabegron OCAS 100 mg tablet po, only daily fasted; Digoxin 0.250 mg tablet po; fasted</p>	<p>25 Healthy volunteers</p>	<p>Digoxin 0.250 mg single dose on day 1; mirabegron 100 mg qd (day 10 to day 23); digoxin</p>

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					0.250 mg single dose in combination with mirabegron dose on day 18
178-CL-040 in France	Effect of mirabegron at steady state on the PK of single dose of warfarin	Phase 1, open-label, 1-sequence crossover	Mirabegron OCAS 100 mg po; once daily fasted Warfarin 25 mg tablet (as five 5 mg tablets) po; once daily fasted	24 Healthy volunteers	Warfarin 25 mg single dose on day 1 washout period of 14 days mirabegron 100 mg qd for 16 consecutive days (day 15 to day 30) warfarin 25 mg single dose on day 23
178-CL-069 in France	Effect of steady state mirabegron on PK of single dose solifenacin and effect of steady state solifenacin on PK of single dose mirabegron	Phase 1, open-label, 1-sequence, 2-arm study	Mirabegron OCAS 100 mg tablet po, once daily fasted Solifenacin 10 mg tablet po; once daily fasted	41 Healthy Volunteers	Treatment arm 1: solifenacin 10 mg single dose day 1 (washout 14 days); mirabegron 100 mg qd day 15 to 38; solifenacin 10 mg single dose in

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					<p>combination with mirabegron dose on day 23 Treatment arm 2: mirabegron 100 mg single dose day 1 (washout 6 days); solifenacin 10 mg qd day 7 to 20; mirabegron 100 mg single dose in combination with solifenacin dose on day 16</p>
<p>178-CL-080 in France</p>	<p>Cardiovascular interactions between mirabegron and tamsulosin</p>	<p>Phase 1, open-label, 2-arm, 2-sequence crossover</p>	<p>Mirabegron OCAS 100 mg po; once daily fasted Tamsulosin 0.4 mg capsule po; once daily fasted</p>	<p>48 Healthy Volunteers</p>	<p>Arm 1, Sequence 1: tamsulosin 0.4 mg on day 2 (washout 22 days), mirabegron 100 mg days 27 to 39, tamsulosin 0.4 mg single dose on day 35 Arm 1, Sequence 2: mirabegron 100 mg</p>

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					days 2-14, tamsulosin 0.4 mg single dose on day 10 (washout 10 days); tamsulosin 0.4 mg single dose on day 27 Arm 2, Sequence 1: mirabegron 100 mg on day 2 (washout 18 days) tamsulosin 0.4 mg days 23- 35, mirabegron 100 mg single dose on day 27 Arm 2, Sequence 2: tamsulosin 0.4 mg days 2-14, mirabegron 100 mg single dose on day 6 (washout 6 days); mirabegron 100 single dose on day 23
Human Pharmacodynamic Studies					

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<p>178-CL-037 in United States</p>	<p>Thorough QT</p>	<p>Phase 1, randomized, double-blind, placebo- and active-controlled, 4-way crossover</p>	<p>Mirabegron OCAS 100 and 200 mg tablet; moxifloxacin 400 mg capsule; matching placebo tablet (mirabegron) and capsule (moxifloxacin) po; once daily fasted</p>	<p>49 Healthy Volunteers</p>	<p>Four 7-day treatment periods; washout of ≥ 10 days between treatments Mirabegron/ matching placebo: 7 days Moxifloxacin: placebo to match mirabegron days 1-6, moxifloxacin/ matching placebo on day 7</p>
<p>178-CL-077 in United States</p>	<p>Thorough QT</p>	<p>Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group, 2-way crossover</p>	<p>Mirabegron OCAS 50, 100 or 200 mg tablet or moxifloxacin 400 mg capsule po; and matching placebo; once daily fasted</p>	<p>352 Healthy Volunteers</p>	<p>Two 10-day treatment periods; washout of ≥ 10 days between treatments</p>
<p>178-CL-053 in France</p>	<p>Cardiovascular mechanistic study</p>	<p>Phase 1, randomized, single blind, 2-arm, 3-way crossover design</p>	<p>Mirabegron OCAS 200 mg tablets (2x 100 mg) po; matching placebo; fasted Propranolol 160 mg capsule (prolonged release) po,</p>	<p>12 Healthy Male Volunteers</p>	<p>Day 1: Propranolol, bisoprolol or placebo followed by mirabegron placebo; Day 5: Propranolol, bisoprolol or</p>

			Bisoprolol 10 mg tablet po ; or matching placebo; fasted		placebo followed by mirabegron 200 mg; minimum of 14 days between each dose of mirabegron
178-CL-081 in United States	Ocular Safety	Phase 1b, randomized, double-masked, 2-arm, parallel group	Mirabegron OCAS 100 mg tablets po; matching placebo; once daily fasted	321 Research subjects (Healthy volunteers or adults with overactive bladder)	56 days

Source: Table 1, Listing of Clinical Studies, CTD module 5.2, page 2

5.2 Review Strategy

The basis of the NDA review will be the 3 EU/NA 12-week phase 3 pivotal studies and the EU/NA Long-term Controlled study. The other studies and data sets will be used secondarily in a supportive manner. Individual studies that evaluated specific safety issues will be analyzed as will adverse events of interest and reports relating to special topics prepared by the Sponsor. This will serve as the basis for analysis of the integrated assessments of efficacy and safety and ultimately for the synthesis and documentation of the overall conclusions.

5.3 Discussion of Individual Studies/Clinical Trials

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

This Phase 3 multinational, multicenter study was conducted at 189 sites in 26 countries in Europe and Australia. A total of 200 sites were initiated; 189 sites enrolled patients.

The primary objective of the study was to assess the efficacy of mirabegron 50 mg once daily

(qd) and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of overactive bladder (OAB). There were 2 secondary objectives: To assess the safety and tolerability of mirabegron 50 mg qd and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of OAB. To compare the efficacy and safety of mirabegron with tolterodine SR 4 mg qd in the treatment of patients with symptoms of OAB.

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

Table 3: Schedule of Procedures Study 178-CL-046

Study Period	Screening		Base-line		Double-blind treatment			Follow-up		
	Week	-2	T†	0	4	8	T†	12	T/V‡	Week 12 +30 days
Visit	1	2		3	4	5		6		
Procedures										
Patient information	X									
Informed consent	X									
Demographics	X									
Medical history and OAB history	X									
Medication history, OAB treatment history	X									
Cough provocation test (women only)	X									
Inclusion/exclusion criteria check	X	X								
Randomization		X								
Study drug dispensing	X	X	X	X	X	X				
Study drug compliance check		X	X	X	X	X				
Concomitant medication	X	X	X	X	X	X			X	
Patient instruction on diary completion, and pulse rate and blood pressure measurement	X	X	X	X	X	X				
Safety										
Physical examination	X						X			
Hematology and biochemistry §	X			X	X	X				
Urinalysis ¶	X									
Pregnancy test ††	X						X			
Vital signs §‡‡	X	X §‡‡	X §‡‡	X §‡‡	X §‡‡	X §‡‡				
Ultrasonography or bladder scan (PVR)	X						X			
12-lead ECG §	X						X			
Adverse events	X	X	X	X	X	X			X	
Efficacy and Pharmacokinetics										
Diary to be completed during 3 days immediately prior to visit		X	X	X	X	X				
OAB-q		X	X	X	X	X				
PPBC, TS-VAS		X					X			
EQ-5D questionnaire		X	X	X	X	X				
WPAI:SHP		X					X			
Data collection on physician visits for the patient's bladder condition (nonstudy-related)		X	X	X	X	X				
Blood sampling for population pharmacokinetics §§				X §§	X §§	X §§				

Source: Scanned Copy Table 1, 178-CL-046 Study Report, Page 44.

2336 patients enrolled and 1987 patients were randomized as follows:

- Full Analysis Set: 1906 patients: placebo 480 patients; mirabegron 50 mg: 473 patients; mirabegron 100 mg: 478 patients; tolterodine SR 4 mg: 475 patients.
- Full Analysis Set- Incontinence (reflecting those randomized patients who had incontinence at baseline): 1165 patients: placebo 291 patients; mirabegron 50 mg: 293 patients; mirabegron 100 mg: 281 patients; tolterodine SR 4 mg: 300 patients.

Study Design

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

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

Prior to commencing the phase 3 clinical trials, the Sponsor, after discussions with the Division of Reproductive and Urologic Products, instituted a method of patient blood pressure self measurement. The patients measured their own blood pressures and pulse rates during the 3 diary days preceding Visits 2, 3, 4 and 5/end of treatment after waking up in the morning and between 2 and 6 p.m. in the afternoon. The blood pressure readings were obtained sitting. Three readings were performed two minutes apart on each occasion.

The co-primary efficacy variables included:

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

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

The key secondary efficacy variables included:

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

Safety variables included:

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

During each office visit, the site recorded vital sign measurements using the patient's self-measurement device and the site's standard office measuring device. Three readings were to be taken approximately 2 minutes apart with each device. The site personnel then calculated the average value for each vital sign parameter using the last 2 of the 3 readings from each measurement device as follows:

Average of self-measurement device (AVGSM) = (measurement 2 + measurement 3)/2

Average of standard office measurement device (AVGSO) = (measurement 2 + measurement 3)/2

Then, the average of the average for each measurement device for each vital sign parameter was calculated as follows:

Average (AVG) = (AVGSM + AVGSO)/2

At baseline, the patient's blood pressure status was used to categorize the patient as either normotensive or hypertensive. A patient was categorized as normotensive at baseline if the average SBP was < 140 mm Hg and the average DBP was < 90 mm Hg at baseline; a patient was categorized as hypertensive at baseline based on the investigator's assessment. For post-baseline assessments, the investigator then used the following criteria, as defined in the protocol, to determine if a patient was considered hypertensive. Assessments were based on blood pressure measurements obtained at the office visits.

1. If the average SBP was \geq 140 mm Hg and/or the average DBP was \geq 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 [World Health Organization, International Society of Hypertension, 2003].

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 to 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 of blood pressure.

Tachycardia was defined as a resting heart frequency > 100 beats per minute (bpm) measured as pulse rate.

Statistical Methods

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

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

Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the $\alpha = 0.025$ level.

Population

In the Safety population, overall, 72.2% of patients were female. The mean age was 60.0 years, with a range of 20 to 95 years of age. The majority (62.9%) of patients were < 65 years of age and 91.3% were < 75 years of age. Overall, 99.1% of patients were white. Mean body mass index across all treatment groups was 27.8 kg/m².

Efficacy results:

Table 4: Efficacy Results Study 178-CL-046

Co-Primary Efficacy Results	Mirabegron		Tolterodine ER 4 mg
	50 mg	100 mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr(FAS-I)			
n	293	281	300
Adjusted mean difference vs placebo(SE)	-0.41 (0.160) p=0.003	-0.29 (0.162) p=0.010	-0.10 (0.159) p=0.11
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
n	473	478	475
Adjusted mean difference vs placebo(SE)	-0.60(0.156) p=<0.001	-0.44(0.156) p=0.005	-0.25(0.156) p=0.11
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
n	472	478	475
Adjusted mean difference vs placebo(SE)	11.9 (2.83) p=<0.001	13.2 (2.82) p=<0.001	12.6 (2.83) p=<0.001
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
n	293	281	299
Adjusted mean difference vs placebo(SE)	-0.39 (0.167) p=0.002	-0.38 (0.169) p=0.002	-0.35 (0.166) p=0.019
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
n	471	477	474
Adjusted mean difference vs placebo(SE)	-0.40 (0.136) p=0.004	-0.52 (0.136) p=<0.001	-0.33 (0.136) p=0.016

Source: Table 1, Summary of Clinical Efficacy, current submission, page 9. For placebo results for co-primary endpoints, see the following 2 tables.

Reviewer’s Comment: The co-primary efficacy endpoint results for tolterodine were smaller than expected, possibly reflecting previous antimuscarinic therapy for OAB with suboptimal result. For mirabegron and for tolterodine, however, statistically significant improvements in both co-primary endpoints were observed at 4 weeks.

Table 5: Change From Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Placebo (n=291)	Mirabegron		Tolterodine
		50 mg (n=293)	100 mg (n=281)	SR 4 mg (n=300)
Baseline				
Mean (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)
Final Visit				
Mean (SE)	1.54 (0.145)	1.22 (0.133)	1.37 (0.134)	1.42 (0.145)
Change From Baseline				
Mean (SE)	-1.13 (0.126)	-1.62 (0.137)	-1.51 (0.115)	-1.21 (0.112)
p-Value		0.003	0.010	0.11
Statistically Superior to Placebo at the 0.05 Level with Multiplicity Adjustment		Yes	Yes	No

Source: Table 17, 178-CL-046 Study Report, page 99.

Table 6: Change From Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo (n=480)	Mirabegron		Tolterodine
		50 mg (n=473)	100 mg (n=478)	SR 4 mg (n=475)
Baseline				
Mean (SE)	11.71 (0.143)	11.65 (0.137)	11.51 (0.124)	11.55 (0.128)
Final Visit				
Mean (SE)	10.35 (0.144)	9.70 (0.139)	9.76 (0.144)	9.97 (0.162)
Change From Baseline				
Mean (SE)	-1.37 (0.115)	-1.94 (0.116)	-1.75 (0.110)	-1.57 (0.123)
p-Value		<0.001	0.005	0.11
Statistically Superior to Placebo at the 0.05 Level with Multiplicity Adjustment		Yes	Yes	No

Source: Table 18, 178-CL-046 Study Report, page 100.

There was no significant treatment group by subgroup interaction for sex, age group (< 75, ≥ 75) and geographic region for the change from baseline to Final Visit in mean number of incontinence episode per 24 hours. The test for interaction by age < 65 versus age ≥ 65 revealed a p-value of 0.078, which the study report describes as “significant”. Table 20 of the

study report appears to show better treatment effect in the older (≥ 65 years) population compared to the younger. Interaction by race could not be performed as 99% of subjects were white.

Table 7: Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours Stratified by Age

Subgroup	Mean Baseline Mirabegron 50 mg (SE)	Placebo N=291	Mirabegron		Tolterodine ER 4 mg N=300
			50 mg N=293	100 mg N=281	
Mean Change from Baseline to Final Visit (SE)					
Age < 65	2.59 (0.205)	-1.12 (0.161)	-1.32 (1.28)	-1.34 (0.171)	-1.23 (0.159)
Age > 65	3.21 (0.246)	-1.14 (0.203)	-2.09 (0.244)	-1.79 (0.189)	-1.19 (0.244)
Age < 75	2.66 (0.164)	-1.16 (0.131)	-1.52 (0.137)	-1.47 (0.137)	-1.26 (0.147)
Age > 75	4.23 (0.671)	-0.85 (0.455)	-2.38 (0.564)	-1.87 (0.351)	-0.74 (0.335)

Source: Tables 12.3.3.2 and 12.3.3.3, Study Report 178-CL-046, pages 462 and 464.

Table 8: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hour Period Stratified by Age

Subgroup	Mean Baseline Mirabegron 50 mg (SE)	Placebo N=480	Mirabegron		Tolterodine ER 4 mg N=475
			50 mg N=473	100 mg N=478	
Mean Change from Baseline to Final Visit (SE)					
Age < 65	11.89 (0.183)	-1.43 (0.148)	-2.13 (0.158)	-1.78 (0.141)	-1.62 (0.159)
Age > 65	11.22 (0.193)	-1.27 (0.184)	-1.61 (0.158)	-1.68 (0.178)	-1.51 (0.192)
Age < 75	11.72 (0.144)	-1.34 (0.122)	-1.96 (0.125)	-1.75 (0.118)	-1.63 (0.127)
Age > 75	10.92 (0.423)	-1.65 (0.364)	-1.79 (0.282)	-1.72 (0.300)	-0.83 (0.434)

Source: Tables 12.3.3.7 and 12.3.3.8, Study Report 178-CL-046, pages 474 and 476.

Reviewer's Efficacy Conclusions: Upon review, the statistically significant efficacy of mirabegron (with correction for multiplicity) for the treatment of OAB has been demonstrated in this study. Mirabegron has also demonstrated efficacy for the key secondary endpoints in this study. The Sponsor has observed that there appeared to be greater efficacy, especially for incontinence episode frequency, in patients >65 years of age compared to those <65 years old. As the two tables above show, there appears to be increased efficacy with regard to mean number of incontinence episodes per day but not for a reduction of mean number of micturitions per day. This resolves a review issue noted at filing.

Safety Results:

Table 9: Overview of Treatment Emergent Adverse Events Study 178-CL-046

	Placebo	Mirabegron		Tolterodine
	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Adverse Events (AE)	214(43.3)	211 (42.8)	199 (40.1)	231 (46.7)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Serious Adverse Events	8 (1.6)	14 (2.8)	12 (2.4)	11 (2.2)
AE leading to Discontinuation	13 (2.6)	24 (4.9)	16 (3.2)	22 (4.4)

Source: Table 32, 178-CL-046, page 128.

The Sponsor summarizes the safety results as follows:

- The overall incidence of patients with TEAEs was similar across the treatment groups (43.3%, 42.8%, 40.1% and 46.7%; placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg, respectively).
- One death, due to a cerebral aneurysm, occurred in a tolterodine SR 4 mg-treated patient 10 days after the last dose of study drug.
- The overall incidence of patients with treatment-emergent SAEs was 1.6%, 2.8%, 2.4% and 2.2% in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively. The overall incidence of patients who discontinued study drug due to a TEAE was 2.6%, 4.9%, 3.2% and 4.4% in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively.
- For events of interest (these are Sponsor’s observations) :
 - The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was higher in the tolterodine SR 4 mg (9.5%) and placebo (9.3%) groups than in the mirabegron 50 mg (7.7%) and 100 mg (6.3%) groups.
 - TEAEs of QTc prolongation in the Torsades de pointes/QT prolongation SMQ were observed only in the tolterodine SR 4 mg group (2 patients, 0.4%). No proarrhythmic findings of ventricular tachycardia, ventricular fibrillation or torsades were reported.
 - The overall incidence of arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 1.0% in the placebo group, 2.2% in the mirabegron 50 mg group, 1.8% in the mirabegron 100 mg group, and 3.2% in the tolterodine SR 4 mg group. For the purposes of classification, these events are classified in the following manner:
 - Atrial Arrhythmia
 - Atrial Fibrillation
 - Supraventricular Tachycardia

Ventricular Arrhythmia

- Ventricular Tachycardia (includes torsades de point)
- Ventricular Fibrillation

High Grade Atrioventricular Block

- 2nd degree Mobitz II
- 3rd degree

The following 5 criteria were used to determine cases of atrial fibrillation of medical importance:

1. The patient did not have a medical history or predose ECG consistent with atrial fibrillation, but developed atrial fibrillation posttreatment as evident on a posttreatment ECG or through reporting of a TEAE of atrial fibrillation.
2. The patient reported a TEAE of new onset atrial fibrillation or worsening atrial fibrillation with a prior medical history.
3. The patient had a baseline (pretreatment) ECG that was "negative for atrial fibrillation," but a posttreatment ECG that was consistent with atrial fibrillation.
4. The patient had a baseline ECG reflective of rate controlled atrial fibrillation (heart rate < 100 bpm) and a posttreatment ECG consistent with atrial fibrillation with poor rate control or rapid ventricular response (heart rate \geq 100 bpm).
5. The patient had a TEAE of potential cardiovascular nature, which was not identified as atrial fibrillation, but was adjudicated by the independent cardiovascular adjudication committee as atrial fibrillation. It should be noted that not all events of treatment emergent atrial fibrillation of medical importance were adjudicated by the cardiovascular adjudication committee. The adjudication committee evaluated all deaths and cardiovascular-related AEs for patients who died or reported any cardiovascular SAE

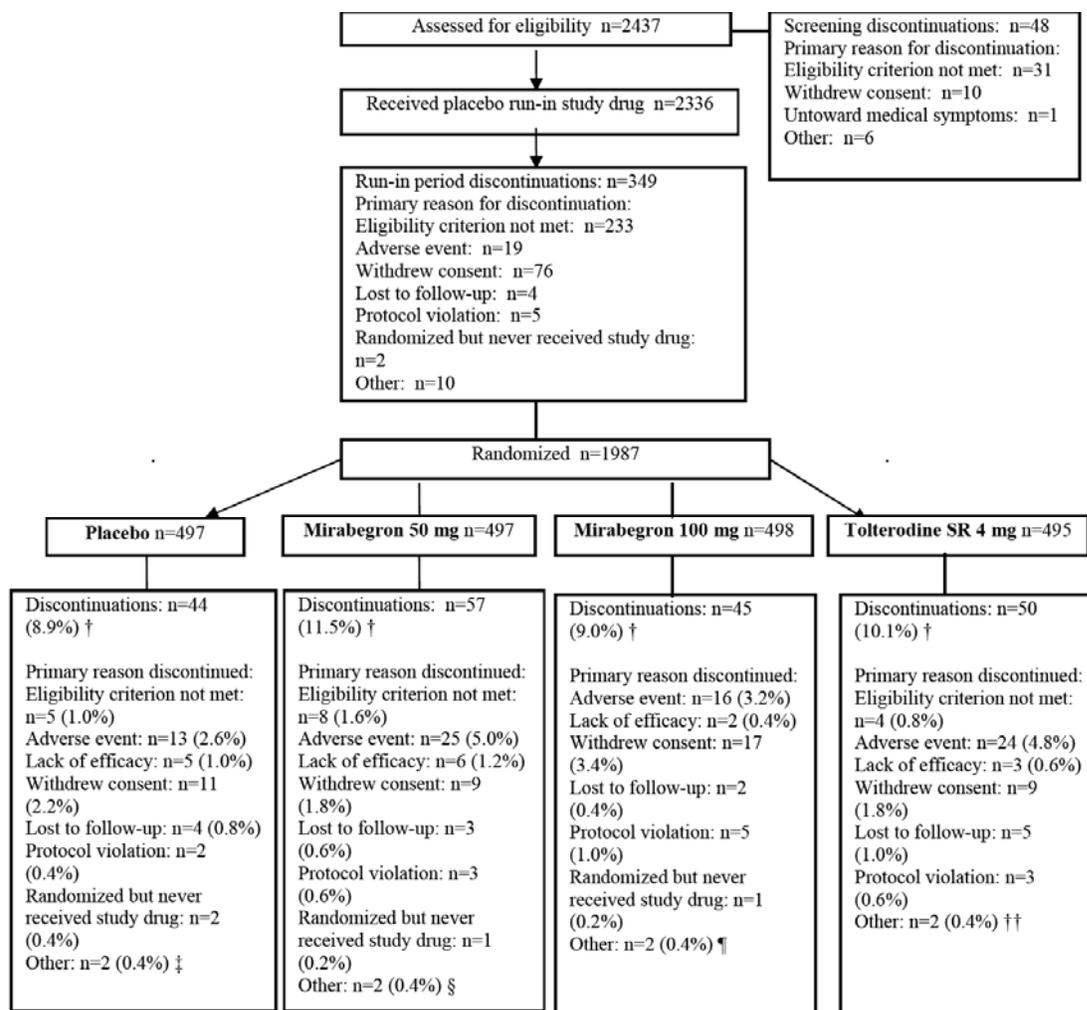
Cases of atrial fibrillation of medical importance were noted in 0 patients in the placebo group, 1 patient in the mirabegron 50 mg group, 2 (0.4%) patients in the mirabegron 100 mg group, and 1 (0.2%) patient in the tolterodine SR 4 mg group. The patient in the mirabegron 50 mg group came into the study with significant cardiac disease (3225-2443). Patient 3014-2243 in the 100 mg mirabegron group had compensated cardiac insufficiency and bronchitis prior to the atrial fibrillation. Subject 3083-2984 had the TEAE of atrial fibrillation. He was 71 years old with a prior history of hypertension. The ECGs at baseline and endpoint did not document atrial fibrillation which had resolved with treatment.

Reviewer's Comment: Of the three reports of atrial fibrillation, only one (3083-2984) was assessed as possibly associated with mirabegron and the dose in this subject was 100 mg, not the marketed dose of 50 mg (for further detail the narratives of Subjects 3225-2443 and 3014-2243 are present under SAEs and Permanent Discontinuations).

- Only 1 patient had a TEAE adjudicated as an APTC/MACE cardiovascular event; Patient No. 1598 in the tolterodine SR 4 mg group experienced cardiovascular death due to a ruptured cerebral aneurysm. The overall incidence of adjudicated non-

- APTC/MACE cardiovascular TEAEs was 0.2%, 0.4%, 0.4% and 0.4% in the placebo, mirabegron 50 mg, mirabegron mg and tolterodine SR 4 mg groups, respectively.
- TEAEs of acute urinary retention were reported for 1 patient in the placebo group, 1 patient in the mirabegron 50 mg group, and 3 patients in the tolterodine SR 4 mg group. No patients had a PVR > 500 mL.
 - The overall incidence of TEAEs indicative of potential hypersensitivity was similar across treatment groups (3.2%, 4.5%, 4.0%, and 4.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively).
 - No episodes of syncope were observed in the study.
 - A TEAE of seizure was reported for 1 (0.2%) patient in the tolterodine SR 4 mg group and no patients in the placebo or mirabegron groups.
 - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders Comprehensive Search SMQ, was similar across treatment groups (1.4%, 2.2%, 1.4% and 2.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively). Most hepatic TEAEs were mild or moderate in intensity.
 - No patients met laboratory criteria for Hy's law. The incidence of patients with hepatic parameters meeting PCS (Potentially Clinically Significant) criteria was 2.2%, 1.2%, 1.4% and 1.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR4 mg groups, respectively (excluding patients with GGT values that met the PCS criterion for GGT only).
 - The incidence of hepatic events when TEAEs and PCS criteria were assessed concurrently was 0, 0.2%, 0.8%, and 1.0% in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively.
 - Changes in hematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups.
 - Dose-dependent increases in adjusted mean placebo-subtracted change from baseline to Final Visit for AM and PM pulse rates were observed with mirabegron treatment compared to placebo (AM: 0.8 and 1.6 bpm; PM: 0.7 and 2.0 bpm for mirabegron 50 mg and 100 mg, respectively). Treatment with tolterodine SR 4 mg resulted in an increase compared to placebo of 0.8 bpm in mean AM pulse rate and 1.9 bpm in mean PM pulse rate.
 - Adjusted mean changes from baseline in systolic and diastolic blood pressure measurements were similar across treatment groups and between normotensive and hypertensive population.
 - Increases in heart rate noted on ECGs were consistent with increases in pulse rate. No consistent ECG trends were identified.
 - The incidence of notable shifts in PVR was comparable across treatment groups. One patient (0.2%) in the mirabegron 50 mg group, 2 (0.4%) patients in the mirabegron 100 mg group, and 1 (0.2%) patient in the tolterodine SR 4 mg group had PVR values > 300 mL at the Final Visit.

Figure 2: Patient Disposition Study CL-178-046



Source: Copy Figure 2, 178-CL-046 Study Report, page 73

Reviewer's Comment: Of the 48 patients who discontinued during screening, 31 did not meet eligibility criteria. There were no discernible trends noted in patient disposition. Of the 349 subjects who discontinued during the Run-in period, 233 did not meet eligibility criteria, 19 experienced an adverse event and 76 withdrew consent. The reviewer does not believe that the discontinuations during the run-in period affects the generalizability of the study findings. Subjects lost to followup once randomized were 0.8% for placebo, 0.6% for mirabegron 50 mg, 0.4% for mirabegron 100mg and for tolterodine ER 4 mg 1.0%. It is doubtful this small incidence of lost to follow-up affects trial outcomes.

There were no deaths in the mirabegron treatment groups.

Table 10: Common TEAEs (>= 2% in any Treatment Group) Study 178-CL-046)

MedDRA (v9.1) Preferred Term	Placebo	Mirabegron		Tolterodine
	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Hypertension	38 (7.7)	29 (5.9)	27 (5.4)	40 (8.1)
Nasopharyngitis	8 (1.6)	14 (2.8)	14 (2.8)	14 (2.8)
Dry Mouth	13 (2.6)	14 (2.8)	14 (2.8)	50 (10.1)
Headache	14 (2.8)	18 (3.7)	9 (1.8)	18 (3.6)
Influenza	8 (1.6)	11 (2.2)	10 (2.0)	7 (1.4)
Urinary Tract Infection	1 (1.4)	1 (1.4)	9 (1.8)	10 (2.0)
Constipation	1 (1.4)	8 (1.6)	8 (1.6)	10 (2.0)

Source: Table 33, 178-CL-046, page 128.

Reviewer's Comment: Headache and nasopharyngitis, thought reported infrequently, appear to be related to treatment with mirabegron 50 mg in this study. 29 subjects (5.9%) were identified with the AE of hypertension in the mirabegron 50 mg group. This is a lower incidence than the reports of hypertension in the placebo group (n=38 patients, 7.7%). All mirabegron patients who reported hypertension were listed in Table 41 (page 145) of Study Report 178-CL-046. 14 of these patients were identified as no prior history of hypertension. The CRFs for these patients were accessed. Blood pressures prior to Day 1 were evaluated. The first day that the blood pressures were measured was not considered. If the patient had multiple blood pressures (on different days) exceeding 140 mmHg systolic or 90 mmHg diastolic, they were considered as having pre-existing hypertension for the purposes of this analysis. This differs from the Sponsor's criteria. 12 of the 14 patients were identified as having pre-existing hypertension. Two subjects appear to have treatment emergent hypertension (3232-2147 and 3353-3411). There were 15 patients in the mirabegron 100 mg group and 13 patients in the placebo group identified as having treatment emergent hypertension. It would appear, therefore, that treatment emergent hypertension in this study was not related to treatment with mirabegron.

A JMP search was performed for terms referring to pre-existing hypertension. The search was performed using the AEDECOD for hypertension and then using the AETERM for terms relating to worsening of hypertension. The only terms found were worsening or worsened in referring to hypertension, arterial hypertension and hypertensive crisis. 8 such cases were found in the mirabegron 50 mg arm, 10 in the mirabegron 100 mg arm and 11 in the placebo arm. The baseline average office determination was used for comparison. Pre-baseline values were surveyed (but not the first pre-baseline visit), for blood pressures above the baseline readings. Post-baseline blood pressures were then

reviewed. Cases where the blood pressure levels exceeded baseline and exceeded the highest pre-baseline levels (based on multiple determinations) were then determined to be a possible “worsening” of hypertension. Of the 8 cases of worsening hypertension identified in the mirabegron 50 arm, there were 3 determined to possibly indicate “worsening hypertension.” The 10 cases in the mirabegron 100 mg arm and the 11 cases in the placebo were not subjected to the same analysis. It is, however, my opinion that worsening of hypertension in patients on mirabegron does not appear to be different than the background level occurring in the placebo population assuming the same percentage of verified “worsening hypertension” is found in these groups.

Reviewer’s Comment: There are no other safety concerns generated by AE analysis.

Table 11: Serious Treatment Emergent Events Study 178-CL-046

MedDRA (v9.1) System Organ Class Preferred Term	Placebo (n=494)	Mirabegron		Tolterodine
		50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Any serious adverse event	8 (1.6)	14 (2.8)	12 (2.4)	11 (2.2)
Infections and Infestations	0	3 (0.6)	1 (0.2)	1 (0.2)
Erysipelas	0	0	1 (0.2)	1 (0.2)
Hepatitis A	0	1 (0.2)	0	0
Postoperative Infection	0	1 (0.2)	0	0
Urinary Tract Infection	0	1 (0.2)	0	0
Injury, Poisoning and Procedural Complications	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)
Fall	0	0	1 (0.2)	1 (0.2)
Humerus Fracture	0	1 (0.2)	0	0
Limb Injury	0	1 (0.2)	0	0
Open Wound	0	0	1 (0.2)	0
Gas Poisoning	1 (0.2)	0	0	0
Lower Limb Fracture	1 (0.2)	0	0	0
Cardiac Disorders	3 (0.6)	2 (0.4)	1 (0.2)	1 (0.2)
Atrial Fibrillation	0	1 (0.2)	1 (0.2)	0
Acute Coronary Syndrome	0	1 (0.2)	0	0
Cardiac Failure Acute	0	0	1 (0.2)	0
Arrhythmia	0	0	0	1 (0.2)
Atrioventricular 1° Block	1 (0.2)	0	0	0
Coronary Artery Disease	1 (0.2)	0	0	0
Myocardial Infarction	1 (0.2)	0	0	0
MedDRA (v9.1)	Placebo	Mirabegron		Tolterodine

System Organ Class Preferred Term	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
<i>Table 18 Continued</i>				
	n (%)			
Gastrointestinal Disorders	0	1 (0.2)	2 (0.4)	1 (0.2)
Abdominal Pain	0	1 (0.2)	0	0
Enterocoele	0	0	1 (0.2)	0
Pancreatitis Chronic	0	0	1 (0.2)	0
Reflux Esophagitis	0	0	1 (0.2)	0
Gastritis	0	0	0	1 (0.2)
Renal and Urinary Disorders	0	2 (0.4)	1 (0.2)	0
Calculus Urinary	0	0	1 (0.2)	0
Nephrolithiasis	0	1 (0.2)	0	0
Urinary Retention	0	1 (0.2)	0	0
Investigations	0	1 (0.2)	1 (0.2)	1 (0.2)
Cardiovascular Evaluation	0	0	1 (0.2)	0
Hepatic Enzyme Increased	0	1 (0.2)	0	0
Catheterization Cardiac	0	0	0	1 (0.2)
Nervous System Disorders	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.4)
Cerebral Ischemia	0	0	1 (0.2)	0
Neuralgia	0	1 (0.2)	0	0
Balance Disorder	1 (0.2)	0	0	0
Epilepsy	0	0	0	1 (0.2)
Ruptured Cerebral Aneurysm	0	0	0	1 (0.2)
Surgical and Medical Procedures	1 (0.2)	0	2 (0.4)	1 (0.2)
Bunion Operation	0	0	2 (0.4)	0
Papilloma Excision	0	0	0	1 (0.2)
Polypectomy	1 (0.2)	0	0	0
Eye Disorders	0	1 (0.2)	0	0
Retinitis	0	1 (0.2)	0	0
Musculoskeletal and Connective Tissue Disorders	0	1 (0.2)	0	0
Rotator Cuff Syndrome	0	1 (0.2)	0	0
Sympathetic Posterior Cervical Syndrome	0	0	1 (0.2)	1 (0.2)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	0	0	1 (0.2)	0
Bowen's Disease	0	0	1 (0.2)	0
Leukemia	0	0	0	1 (0.2)
Pregnancy, Puerperium and Perinatal Conditions	0	1 (0.2)	0	0

Pregnancy	0	1 (0.2)	0	0
Reproductive System and Breast Disorders	0	0	1 (0.2)	0
Rectocele	0	0	1 (0.2)	0
Vaginal Erosion	0	0	1 (0.2)	0

MedDRA (v9.1) System Organ Class Preferred Term <i>Table 18 Continued</i>	Placebo (n=494)	Mirabegron		Tolterodine
		50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Vascular Disorders	0	1 (0.2)	0	0
Hypertensive Crisis	0	1 (0.2)	0	0
Hypertension	0	0	0	1 (0.2)
General Disorders and Administrative Site Conditions	2 (0.4)	0	0	0
Asthenia	1 (0.2)	0	0	0
Chest Pain	1 (0.2)	0	0	0
Pyrexia	1 (0.2)	0	0	0
Hepatobiliary Disorders	0	0	0	1 (0.2)
Hepatitis	0	0	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorder	0	0	0	1 (0.2)
Asthma	0	0	0	1 (0.2)

Source: Table 36, 178-CL-046 Study Report, page 130.

Reviewer's Comment: The overall incidence of SAE's is modestly higher for mirabegron patients. No SAE, except for "bunion operation" was reported by more than 1 patient. This review does not indicate disproportionate reporting in any one SOC or any group of SOCs.

Selected SAE Narrative in Brief:

Subject 3355-3411: Hepatitis A: The subject is a 32 year old white Spanish male randomized to mirabegron 50 mg. The subject received study drug for a total of 84 days. Study drug was not discontinued due to any adverse event. On Day 107 the patient was hospitalized with symptoms of fever and jaundice and diagnosed with hepatitis A. The subject's serology test was positive for IgM HAV. On Day 185, the subject was reported to have recovered hepatitis A. There was no medical history indicative of a predisposition for infection, an additional event the subject experienced was hypertension from Day 53, reported as ongoing at the time of study completion.

Reviewer's Comment: I cannot attribute causality of this SAE to mirabegron.

Subject 3297-2448: Erysipelas: The subject is a 79 year old white British female randomized to mirabegron 100 mg. The subject received a total of 79 days of study drug. The study treatment was not discontinued due to the adverse event of erysipelas. The patient had no medical condition or medication predisposing to infection. On day 24, the subject reported being unwell for two days. She experienced a red and swollen face, headache, and swelling of the eyelids. She received paracetamol and chlorpheniramine maleate of unknown dosage as corrective treatment. The condition of the subject worsened and the subject was hospitalized and the event diagnosed as erysipelas. The subject received benzylpenicillin and flucloxacillin intravenously (dose and frequency unknown) for the treatment of the event. On Day 24 the ALT was elevated to 47 U/L with return to normal range by Day 52 (19 U/L). There was no documented increase of eosinophils and on Day 24 the eosinophil count was 0.

Reviewer's Comment: I cannot attribute causality of this SAE to mirabegron considering this event in isolation. All infectious adverse events will be considered together as part of the Integrated Summary of Safety (ISS) which appears later in this review.

Subject 3225-2785: Postoperative Infection: The subject is a 63 year old white Norwegian male randomized to mirabegron 50 mg. The subject received a total of 34 days of study drug. The study drug was discontinued due to the adverse event of postoperative infection after cholecystectomy (Day 30) on Day 34. The patient had known gallstones present prior to study enrollment. There was no medical history or concomitant medication predisposing to infection. The subject was reported as recovered from the event on Day 47.

Reviewer's Comment: I cannot attribute causality of this SAE to mirabegron considering this event in isolation, especially considering the patient's known history of gallstones.

Subject 3018-1731: Urinary Tract Infection: The subject is a 59 year old white German male randomized to mirabegron 50 mg. On Day 48, the patient experienced acute urinary retention. The patient was taking tamsulosin 0.4 mg a day. On Day 50, he experienced the adverse event of urinary tract infection. He had a known history of a prostate adenoma. His PVR at Day -15 was 59 mL. On an unspecified date, the subject's prostate specific antigen was elevated to 6.2 ng/L. He was additionally experiencing macrohematuria. On an unspecified data a prostate biopsy was reported negative for malignancy. Study drug was discontinued on Day 48. Cystourethroscopy was performed on Day 49. On Day 54 and 57, the subject is reported recovered from acute urinary retention and UTI, respectively. The report contains no detail about catheterization or PVR if a catheter was inserted. On Day 70, the subject underwent a transurethral resection of the prostate. He is reported recovered.

Reviewer's Comment: The urinary retention and UTI in this case could be related, at least in part, to treatment with mirabegron. It is notable that the patient was male and was already taking tamsulosin, apparently for bladder outlet obstructive symptoms.

Subject 3063-3301: Fall: The subject is a 79 year old white French female randomized to mirabegron 100 mg 6 November 2008. The patient has a history of falls due to balance disorders (since 2008-02) and Parkinson's disease (since 2008-02). She is taking valsartan, urapidil, candesartan and lercanidipine for hypertension and venlafaxine for depression. On Day 71, the subject lost balance and fell. There is no history of syncope or presyncope. She did have a first degree heart block on baseline ECG. There were no acute changes in vital signs or ECG while on study treatment. There were no documented injuries. The event was considered resolved on Day 79. Study drug was not discontinued.

Reviewer's Comment: In light of confounding conditions (history of falls due to balance disorders), I cannot attribute this SAE to the study drug.

Subject 3232-2481: Fracture Humerus: The subject is a 67 year old white Swedish male randomized to mirabegron 50 mg. The patient noted disturbance of attention from Day 2 to Day 50. On Day 40, the subject was kicked by a horse and experienced a fractured right humerus. There is no documentation of negligent behavior by the patient. The patient completed drug therapy on Day 80. The outcome is recovered.

Reviewer's Comment: It is notable that the patient experienced a fractured right humerus after being kicked by a horse. While I cannot attribute this SAE to study drug, disturbance of attention could lead to accidental injury and this AE will be better assessed in the ISS. In evaluating the totality of the safety results, I could not find such an association.

Subject 3072-3069: Limb Injury: The subject is a 43 year old white French male randomized to mirabegron 50 mg. There is no significant medical history or concomitant medications relative to the SAE. The patient's last dose of study drug was Day 91. On Day 109, the subject experienced a left forefinger injury requiring surgery on Day 110. There were no significant other AEs noted. The outcome is recovered.

Reviewer's Comment: I cannot attribute causality to the study drug for this SAE. Sponsor was asked for additional information relating to state of fatigue and attention at the time of injury. In an information response, 9 December 2011, no additional information was available. In this NDA, fatigue and inattention were not reported as adverse reactions to mirabegron.

Subject 3193-3404: Open Wound: The subject is a 56 year old white Finnish male randomized to mirabegron 100 mg. Medical and medication history are not significant. On Day 71, the subject experienced a cut to his left fifth finger with a knife. He was hospitalized and underwent surgery for a damaged nerve. The outcome for the SAE is recovered. The study drug treatment was not discontinued.

Reviewer's Comment: I cannot attribute causality to the study drug for this SAE. Sponsor was asked for additional information relating to state of fatigue and attention at the time

of injury. In an information response, 9 December 2011, no additional information was available. Again, changes in mental acuity were not noted among the adverse reactions to mirabegron in this NDA.

Subject 3225-2443: Atrial Fibrillation: The subject is a 66 year old Norwegian white male randomized to mirabegron 50 mg. The study drug was discontinued on Day 81 due to the SAE of atrial fibrillation occurring on Day 81. The medical history included hypertension (since 1995), elevated blood lipids, obesity and type 2 diabetes (since 2000). Medications included metformin, insulin, simvastatin and lisinopril/hydrochlorothiazide.

On day 60, the subject with a relevant history of obesity and hypertension experienced the first of a total of three adverse events of atrial fibrillation. The subject had no known history arrhythmias. No changes were made to the study drug therapy due to the event. The first event of atrial fibrillation was reported as resolved on day 81. On day 81, the subject went to visit his own physician and was diagnosed with the second adverse event of atrial fibrillation with a heart rate of 140-170 bpm which was assessed as serious. The subject was hospitalized for possible electrocardioversion for atrial fibrillation on the same day (day 81). Physical examination findings at the time of admission to the hospital indicated the subject was in general good health with pronounced obesity, increased blood pressure of 142/77 mmHg, irregular pulse of 170 bpm, irregular heart and lungs with normal vesicular breath sounds. Laboratory results showed internalized normalized ratio of 1.7, potassium 5.0, blood thyroid stimulating hormone 1.39, thyroxine total circulating 15, and triiodothyronine total circulating 3.6 (no units or reference ranges provided). Chest x-ray revealed an enlarged heart, possible slight prominence of pulmonary vessels, no edema or CHF, nonspecific diffuse changes in right base. ECG findings at Day 81 were atrial fibrillation with ventricular rate of 155. Due to the low INR value, it was not appropriate to cardiovert the subject during the hospital stay ((b) (6) hospital records). Study drug was discontinued due to the serious adverse event of atrial fibrillation on day 81. The subject was discharged and the serious adverse event of atrial fibrillation was reported as resolved on day 86.

After discharge from the hospital, ongoing from day 86, the subject continued to experience atrial fibrillation, which was reported as the third adverse event of atrial fibrillation. Physical examination of the subject on day 102 indicated atrial fibrillation and the result was reported as changed and clinically significant. On day 102, adverse event of increased total bilirubin was reported. Additionally, ALT and GGT values were above the upper limit of normal on day 102. The adverse event of total bilirubin was reported as not resolved at the time of study completion. Pertinent negatives include no reported icterus, jaundice, nausea, vomiting or abdominal tenderness.

The subject was hospitalized a second time on day 112 ((b) (6)). Upon admission the subject had blood pressures of 182/62 mmHg and 145/80 mmHg, pulse 77 bpm, the condition of the heart was reported as irregular with no definite murmurs and lungs, with normal vesicular breathing showed no definite pathological sounds (RR: 16, SaO2: 97%), and ECG on day 112 demonstrated sinus tachycardia of 79 bpm with bigeminal rhythm and no sign of atrial fibrillation upon admittance ((b) (6) discharge summary). ECG findings at Day 112 were

sinus tachycardia 79 bpm with bigemini rhythm. The last episode of paroxysmal atrial fibrillation was on day 125. The event of atrial fibrillation was reported as resolved on day 125.

This case was sent to the independent cardiovascular adjudication committee which concluded that it was a non- APTC/MACE cardiovascular event of atrial fibrillation with no evidence of ischemia.

Reviewer's Comment: Although the patient had multiple cardiac risk factors, a causal association with mirabegron in this individual case cannot be ruled out. The increased liver chemistries on Day may be attributable to the multiple medications used to treat the atrial fibrillation.

Subject 3014-2243: Atrial Fibrillation, Cardiac Failure Acute: The subject is a 90 year old white German female randomized to mirabegron 100 mg on [REDACTED]^{(b) (6)}. On Day 79, study treatment was discontinued due to the serious adverse events of acute cardiac insufficiency and atrial fibrillation. Relevant medical history includes compensated cardiac insufficiency (since 1 March 2008) and bronchitis since 28 August 2008. The patient was taking olmesartan for cardiac insufficiency (since 1 April 2008).

The subject developed a common cold, experienced increasing dyspnea the last three days as well as lower leg edema, and was brought to the emergency room on day 80 where the emergency physician noted that the subject's heart rate was 140 beats/min. After intravenous metoprolol and flecainide were given, the subject was found to have atrial flutter with irregular conduction (heart rate about 90 beats/min). The subject was subsequently hospitalized from day 80 to day 89.

On admission, the subject's general condition and nutritional status were good. She was alert and oriented with temperature of 36.9°C, dyspneic, and non-cyanotic with a pO₂ saturation of 96% (not specifically mentioned if on room air). Physical examination revealed vesicular breath sounds with bilateral pulmonary rales, normal heart rate, irregular heart rhythm, clear heart sounds, BP of 105/80, and bilateral lower leg edema. Admission chest x-ray demonstrated an enlarged cardiac shadow as well as a small pleural effusion on the left. There was no evidence of myocardial infarction with a normal troponin level [REDACTED]^{(b) (6)} hospital discharge summary).

During hospitalization, inhalation treatment and acetylcysteine were utilized which improved the pulmonary symptoms of bronchitis. Furosemide 40 mg was started and the lower leg edema of the cardiac insufficiency resolved. The atrial flutter that was initially noted on admission had converted to atrial fibrillation. The subject was given phenprocoumon for an unspecified period of time, but because of a history of frequent falls, this was changed to acetylsalicylic acid. The discharge diagnoses included acute bronchitis and new onset of atrial fibrillation [REDACTED]^{(b) (6)} hospital discharge summary).

On day 80, the blood lactate dehydrogenase level was 245 U/l (135-214 U/l) and C reactive protein was 24.3 mg/L (up to 5 mg/l). On the same day, a chest X-ray in 2 planes showed the heart was slightly enlarged with no signs of congestion and occasional residual scarring with no

evidence of acute infiltrates. There was a suspicious small pleural effusion on the left and mild degenerative changes of the dorsal vertebral spine ((b) (6) hospital discharge summary). On an unspecified date during hospitalization, an ECG demonstrated atrial fibrillation with a heart rate of 79 bpm, normal position, and no disturbance of repolarization.

An echocardiography done on an unspecified date during hospitalization revealed dilated LA and RA, normal global systolic left ventricular function with borderline concentric LV hypertrophy, no unequivocal ventricular wall motion abnormality, significantly sclerotic AML (anterior mitral leaflet) and PML (posterior mitral leaflet), mild mitral valve stenosis, moderate MR, markedly sclerotic aortic valve margins with normal separation, mild AR, mild TR, PAP 30 mm Hg, collapsed vena cava, and no pericardial effusion (b) (6), hospital discharge summary). Average vital signs recorded at study visits Week 4 and Week 8 were blood pressure 132/74 and 133/73 mmHg respectively. Heart rates are 82 bpm for Week 4 and 84 for Week 8.

The study treatment was discontinued due to the serious adverse events of acute cardiac insufficiency and episode of atrial fibrillation. The last dose of study drug was given on day 79. On day 90, the subject recovered from the events of acute cardiac insufficiency and episode of atrial fibrillation. The subject recovered from the event of acute bronchitis on a date not provided.

The case of acute cardiac insufficiency was sent to the independent cardiovascular adjudication committee, but the committee indicated that there was insufficient information to adjudicate the event. The case of episode of atrial fibrillation was sent to the independent cardiovascular adjudication committee and the committee indicated that this was atrial fibrillation without evidence of ischemia.

Reviewer's Comment: The history of previous heart failure may have rendered the patient more susceptible for a repeat episode in association with atrial fibrillation. In addition, the patient had clinically significant acute bronchitis, which may have played some role in the occurrence of the arrhythmia.

Subject 3028-2466: Acute Coronary Syndrome: Hypertensive Crisis: The subject is a 62 year old white German female randomized to mirabegron 50 mg (b) (6). On Day 24 the patient experienced angina and hypertensive crisis and the study drug was discontinued. Her medical history includes hypertension (since 1988), and diabetes mellitus (since 1987). Her medications included metformin, talinolol and pentaerythritol tetranitrate.

On day 13, the subject was hospitalized for the serious adverse event of hypertensive crisis. The subject had a relevant medical history of hypertension. Blood pressure readings during screening included: 188/96 mmHg on Day -5, 190/91 mmHg on Day -4, and 182/92 mmHg on Day -3. Blood pressure on the day of admission (day 13) was 170/90 mmHg. CT of the head demonstrated no acute changes; however changes consistent with microangiopathy were noted. An ECG was unremarkable with sinus rhythm at 75 bpm and no disturbances in repolarization (hospital records (b) (6)). The 24-hour blood tests performed due to the blood pressure crisis revealed normal electrolytes and epinephrine as well as normal norepinephrine values. The

protein 24-hour excretion in urine was normal and no secondary cause was found for the arterial hypertension ((b) (6) hospital records). On Day 28, the event of hypertensive crisis was reported as resolved and the subject was discharged from the hospital on Day 29.

On Day 21, a left heart catheterization was performed and revealed 70% LAD stenosis and 60% proximal and medial RCX stenosis. This was reported as an adverse event of two-vessel coronary disease. No coronary intervention was performed. A stress echocardiography done on day 25 showed good sonification with no electrocardiographic or echocardiographic pathological findings. Study drug therapy was discontinued due to the events of hypertensive crisis and angina on day 24. A 24-hour Holter monitor did not demonstrate arrhythmia nor significant blood pressure excursions.

On Day 35, the subject was hospitalized due to suspected acute coronary syndrome; the adverse events of angina as well as dyspnea on exertion were also reported. Heart examination did not show any pathological findings, blood pressure was 150/80 mmHg, and heart rate was 72 beats/min. Cardiac echocardiography demonstrated normal cardiac chambers without left ventricular hypertrophy and without regional dyskinesia. A normal left ventricular ejection fraction was reported (hospital records (b) (6)). A carotid ultrasound demonstrated bilateral changes in the bulb of the right internal carotid as well as left proximal internal carotid artery, neither of which necessitated intervention (hospital records (b) (6)). The serious adverse event of suspected acute coronary syndrome was reported as resolved with sequelae on day 41.

Additional adverse events experienced by the subject included angina starting on day 6 and continuing until after the end of the study and hypothyroidism from Day 13 to Day 35.

The case for the event of hypertensive crisis was sent to the independent cardiovascular adjudication committee, which concluded that this was a serious non-MACE cardiovascular event. The case for the event of acute coronary syndrome was sent to the independent cardiovascular adjudication committee, which concluded that it was a Non-APTC/MACE Cardiovascular Event of confirmed unstable angina.

Reviewer's Comment: The medical history in this case demonstrates that the patient's hypertension was poorly controlled during the screening phase of the Study and while on mirabegron there were no documented vital signs worse than baseline. Sponsor states that the clinical presentation and blood pressure values were not consistent with hypertensive crisis. I agree. As to the adverse event of acute coronary syndrome, the event occurred eleven days after the discontinuation of mirabegron and it is likely that poorly controlled cardiac risk factors contributed to deterioration in cardiac status. The attribution of acute coronary syndrome to study drug is confounded.

Subject 3036-1834: Vomiting, Dizziness, Hypertensive Crisis: Subject is a 69 year old Swiss female randomized to mirabegron 50 mg 27 August 2008. Her medical history includes nephrolithiasis (unknown date), arterial hypertension (since 1971-12), recurrent urinary tract infections (2004 through 2008-08-11), sporadic diarrhea (since 2004), anterior colporrhaphy

(2004- 11-30), hysterectomy (2004-11-30), transobturator tape (2004-11-30) and overactive bladder (since 2003-08). Her concomitant medications include bisoprolol, valsartan, torasemide for blood pressure control and loperamide (for diarrhea). The subject received a total of 29 days of study drug.

On day 24, the subject experienced an adverse event of hypertensive crisis. At that time her highest blood pressure reading was 184/77 mmHg on the last of three am determinations. Her baseline morning and afternoon blood pressures were 168/73 and 125/66 mmHg respectively. The subject had a relevant medical history of hypertension (since 1971-12) and was medically managed with multiple antihypertensives. The subject received furosemide for a total daily dose of 20 mg orally on day 24 for the adverse event of hypertensive crisis. The adverse event of hypertensive crisis was reported as resolved on day 28. At that time her blood pressure readings were (Week 4 were 155/81 and 136/77 mmHg. Study treatment was discontinued on day 29 due to the adverse events of emesis, dizziness and hypertensive crisis.

Reviewer's Comment: I have reviewed the blood pressure readings in the patient CRF, and I agree with Sponsor that the blood pressure readings are not consistent with a hypertensive crisis. There does appear to be an upward trend in the blood pressure in this patient after starting mirabegron. The relationship of the emesis and dizziness to the blood pressure elevations is not known. I would classify this event as worsening of pre-existing hypertension which could be attributed to mirabegron and not as hypertensive crisis.

Subject 3203-1780: Abdominal Pain: Subject is a 50 year old Danish white female randomized to mirabegron 50 mg (b) (6). The patient was taking sertraline for depression. The study drug was not discontinued due to SAE and last day of study drug was Day 84. On Day 86, the subject experienced a serious adverse event of abdominal pain. The subject was hospitalized for the event on day 90. Ultrasound showed no gallstones or pathology in the liver or pancreas. There were no associated laboratory abnormalities reported. The event was considered resolved after initiating treatment with oral pantoprazole, at a total daily dose of 40 mg on day 91 and on the same day the subject was discharged from the hospital.

Reviewer's Comment: A causal association with mirabegron cannot be ruled out, but the event did occur two days after mirabegron discontinuation.

Subject 3015-1967: Enterocoele, Rectocoele, Vaginal Erosion: Subject is a 56 year old white German female who was randomized to mirabegron 100 mg. She completed the 84 Days of the drug study. She is status post a hysterectomy in 2003 and a tension-free vaginal tape procedure for incontinence in 2006. On Day 96, the subject experienced serious adverse events of enterocoele, rectocoele and suburethral vaginal erosion. With estradiol topical treatment the events were listed as resolved on Day 102.

Reviewers' Comment: With the previous gynecologic surgical procedures which can predispose to the SAEs listed, I cannot attribute these SAEs to mirabegron.

Subject 3140-1859: Pancreatitis Chronic: Reflux esophagitis: The subject is a 53 year old white Hungarian female randomized to mirabegron 100 mg [REDACTED]^{(b) (6)}. The subject has a history of chronic pancreatitis and reflux esophagitis (both since 2000).

On day 38, the subject was hospitalized for the serious adverse events of worsening chronic pancreatitis and worsening reflux esophagitis. The study drug therapy was interrupted due to the serious adverse events of worsening chronic pancreatitis and worsening reflux esophagitis. Primary symptoms included obstipation, stomach ache, colic and nausea. In addition to the concomitant medications, the subject was given physiological infusions and was placed on dietary restrictions. The Sponsor in their response of 9 December 2011 to an information request provided the following hospital laboratory data: amylase 86 (Normal range <220 U/L), lipase 35 (Normal range <190 U/L). The bilirubin, AST, ALT and GGT were within the normal range. The managing physician ascribed the patient's GI symptoms to constipation likely due to antidepressants. It is noted that the patient's symptoms resolved with dietary restrictions and laxatives. The adverse event of cystitis was reported resolved on day 42. The serious adverse events of worsening chronic pancreatitis and worsening reflux esophagitis were reported as resolved on day 47. The subject completed the study drug therapy on day 84.

Reviewer's Comment: While the patient's symptoms still could have been due to an exacerbation of underlying chronic pancreatitis, the lack of enzymic confirmation makes this event possible but unlikely. The event resolved despite continued study drug administration.

Subject 3117-3373: Calculus Urinary: The subject is a 50 year old white Polish female randomized to mirabegron 100 mg [REDACTED]^{(b) (6)}. The patient has a past history of nephrolithiasis of the left kidney (1976-March 2006). She had right nephrectomy in 1999 (nephrosclerosis). There is no documentation of stone free status of the left kidney prior to study.

On day 40 the subject was hospitalized for a serious adverse event of urolithiasis. Relevant laboratory results are reported in Table 2. Calcium and uric acid level were within normal limits throughout the study. On day 41, the subject underwent endoscopic ureterorenoscopic lithotripsy to treat the event. The subject received cefuroxime (total daily dose of 750 mg orally) as prophylaxis for a possible urinary tract infection and diclofenac (total daily dose of 100 mg rectally) for pain after an endoscopic ureterorenoscopic lithotripsy. The event of urolithiasis was reported as resolved on day 44, and no changes were made to study drug therapy due to the serious adverse event of urolithiasis. The subject completed study drug therapy on day 84.

Reviewer's Comment: The patient has a significant past medical history of nephrolithiasis. We do not know when the patient's new stone was formed. We only know when the stone began to move from the kidney to the ureter as clinical presentation. I cannot attribute this SAE of urolithiasis to mirabegron. The timing of the stone migrating to the ureter may be coincidental.

Subject 3025-1742: Nephrolithiasis: The subject is a 56 year old German white male randomized to mirabegron 50 mg. The subject received 57 days of study drug which was discontinued due to the adverse event of left renal calculus. The patient has a past history of right renal calculus known since 31 January 2000. The patient had normal serum calcium and urate levels on Day 56. The renal calculus on the left was removed by uterorenoscopy on day 63 and the event was reported as resolved on day 63.

Reviewer's Comment: The patient has a past medical history of nephrolithiasis. As a single event, I cannot attribute the new stone to mirabegron. We do not know when the new left renal calculus actually formed. The timing of the stone migrating to the ureter may be coincidental.

Subject 3403-3124: Cardiovascular Evaluation: The subject is a 57 year old white Romanian female randomized to mirabegron (b) (6). The subject's history includes obesity (since 1985), dyslipidemia (since 2005-February), high blood pressure (since 2005-February) and ischemic cardiopathy (since 2005-February). The subject received study drug for a total of 83 days and completed the study. The patient is maintained on nicergoline, perindopril, acetylsalicylic acid, trimetazidine, and bisoprolol indapamide for high blood pressure and ischemic cardiopathy.

On day -19, the subject's physical examination was significant for obesity. On an unspecified day in 2008-12, the subject experienced an adverse event of hypertension (increase/change in antihypertensive drugs dosage). The event was considered resolved on an unspecified day in 2008-12. The subject's average vital signs were provided in the study report and were evaluated by the reviewer. The investigator considered the event of hypertension to be mild and possibly related to the study drug. Blood pressures were relatively consistent throughout the study and were similar to pretreatment values. Baseline, Week 4 and Week 8 blood pressures were 132/88, 125/91, and 130/87 respectively.

On day 52, the subject was hospitalized for routine annual cardiac evaluation. The serious adverse event of routine hospitalization for annual cardiac evaluation was reported as resolved on day 55. On the same day, the subject was discharged.

Reviewer's Comment: Mirabegron was not causal for this event.

Subject 3312-3435: Hepatic Enzyme Increased: The subject is a 53 year old white Irish female randomized to mirabegron 50 mg 1 November 2008. The subject received study drug for a total of 74 days. Study treatment was discontinued due to the serious adverse event of elevated liver enzymes on day 74. The patient has a past history of elevated liver enzymes (1997-09-25 through 2000-04-20). She also has had a silent MI found on screening ECGs (age undetermined).

On day 60, the subject experienced a serious adverse event of elevated liver enzymes. Study drug was discontinued to this event on day 74 and the event was reported to be resolved on day 94. Pertinent negatives include no reported icterus or jaundice. The patient's GGT was marginally elevated at screening (35 [NL 6-32 U/L]). The AST was 28 (NL 1-32 U/L) at screening. At Day 60, the GGT was 41 and at Day 81 it was 54. By Day 94 the GGT was 38. For the same study days (Screening, Days 60, 81, 94), the AST was 28, 50, 31 and 30 U/L (NL 1-32 U/L). The ALT was 30 U/L at baseline (NL 10-30), 63 at Day 59, 33 at Day 81 and 31 at day 94. The bilirubin and alkaline phosphatase were in normal range throughout the study. The patient had received single intravenous doses of midazolam and pethidine 24 October 2008 for a polyp (intestinal? [not specified in narrative]) removal. In my opinion, these are unlikely causes of liver enzyme elevation in this patient.

Reviewer's Comment: It is notable that the patient has a past medical history significant for elevated liver enzymes. In light of the dechallenge results, causality to mirabegron for this very mild elevation of liver enzymes in patient with possible hepatic compromise cannot be completely ruled out. .

Subject 3065-1702: Cerebral Ischemia: Subject is a 76 year old French female randomized to mirabegron 100 mg (b) (6). The subject received a total of 91 days of study drug. The study treatment was interrupted due to adverse event of cerebral ischemia. The medical history included drug hypersensitivity/allergy to non-steroidal anti-inflammatory medication, allergy to penicillin, drug intolerance to dextropropoxyphene/acetaminophen and tiroprium, anxiety (since 2001), arteritis of lower limbs (since 2001), cardiac arrhythmia (since 2001), carotid artery stenosis (since 2001), diabetes (since 2001), hypercholesterolemia (since 2001), hypertension (since 2001), and pneumopathy (since 2001), esophagitis (since 2005). The patient is maintained on 18 medications for arteritis, diabetes, hypertension, pneumopathy, hyperlipemia, esophagitis, osteoporosis and anxiety.

On day 31, the subject experienced a serious adverse event of possible medullary ischemia. On day 33, the subject was hospitalized for possible medullary ischemia. Physical examination on admission revealed paraparesis (could not walk without support or move legs off bed). The only tendon reflexes perceived on physical examination were the patellar and biceps reflexes, which were symmetrical. Clonus of both feet was seen, even though the subject was complaining of dysesthesia in the back of both feet. No tremors were seen (b) (6) neurology consultation, hospital records). In 2008-09 (date not provided), a CT scan of the head was normal. The first cerebral MRI performed (date not provided) revealed hypersignals at different STIR sequences of the marrow that may be compatible, given the vascular risk factors, with diffuse medullary ischemia. There was a clear cervical and lumbar constriction but which did not seem sufficient to explain the clinical signs after the discussion with the neurosurgeons in the hospital (b) (6) neurology consultation, hospital records). On an unknown date, an MRI was performed with diffusion-weighted sequences which strengthened the hypothesis of medullar ischemia; however, the interpretation of this MRI was highly limited by motion artifacts. Moreover, the anomalies in T2 STIR found on the first MRI disappeared, and this did not allow drawing a final conclusion: the most probable hypothesis was that of moderate medullary ischemia with rapidly regressive effect (b) (6) neurology consultation, hospital records).

On day 39, the subject also experienced an adverse event of hyperkalemia with a serum potassium level of 5.7mmol/L. The subject was treated with sodium polystyrene sulfonate orally for a total daily dose of 15 g. The study treatment was interrupted due to the adverse events of possible medullary ischemia and hyperkalemia (5.7mmol/l). The events of possible medullary ischemia and hyperkalemia (5.7mmol/l) resolved on day 39. On day 39, the subject was discharged from the hospital. The subject was hospitalized again from day 39 to day 50 in the neurology unit. On day 47 [REDACTED] (b) (6), an MRI of the head revealed the T2 sequence did not reveal signal anomaly at the dorsolumbar level. The sagittal cross-sections from the diffusion weighted sequence were difficult to interpret due to motion artifact. There was bilateral foraminal stenosis at the cervical level without anomaly of the intra-medullary signal [REDACTED] (b) (6) (neurology consultation, hospital records). The event outcome is recovered.

This case of possible medullary ischemia was sent to the independent cardiovascular adjudication committee which concluded that it was a Non-APTC/MACE Cardiovascular Event or other serious non-MACE cardiovascular event.

Reviewer's Comment: In light of this patient's complex medical history (including carotid artery stenosis, hypertension, and evidence on MRI of diffuse medullary ischemia and bilateral foraminal stenosis) and large number of medications, I have difficulty attributing any of the events to mirabegron.

Subject 3072-2011: Neuralgia: The subject is a 73 year old French white female randomized to mirabegron 50 mg 4 September 2008. The subject received a total of 91 days of study drug. Study treatment was not discontinued due to any adverse event. Among other diagnoses the patient has a history of hypercholesterolemia (since 1993), hypothyroidism (since 1993), fibromyalgia (since 1997), and Sjögren's Syndrome International Collaborative Clinical Alliance (SICCA) syndrome with mouth and eye dryness (since 1997). She is maintained on 15 medications.

On day 70, the subject experienced a serious adverse event of crural (femoral) neuralgia. The event of femoral neuralgia was treated with morphine sulfate. The event was reported as resolved on day 86. The subject completed the study with last dose received on day 91.

Reviewer's Comment: This case is confounded by the history of fibromyalgia which provides an alternative etiology for the event, making attribution to mirabegron doubtful.

Subject 3018-1633: Retinitis: The subject is an 83 year old white German male randomized to mirabegron 50 mg. There is no relevant medical history. Medications include tamsulosin and ASA.

On Day 60, the subject developed a visual disturbance of his right eye which was diagnosed as retinitis – amotio retinae (detachment of retina) with macular involvement and after cataract. Study drug was interrupted due to this serious adverse event from Day 60 to Day 63. Subject was

hospitalized on Day 61 and underwent pars plana vitrectomy with pseudophakia. On Day 63, the subject recovered from retinitis.

Reviewer's Comment: I cannot attribute causality to mirabegron for this event.

Subject 3298-1247: Bowen's Disease: The subject is a 74 years old British white female randomized to mirabegron 100 mg 12 July 2008. The subject's relevant medical history included basal cell carcinoma over her forehead which was excised in 2005. It was reported that it was successfully treated. The subject also had a relevant medical history of skin lesions and the subject was on topical hydrocortisone cream, started on day -25 twice a day as a treatment for skin lesions. On an unknown date in 2008-08, the subject developed a serious adverse event of a skin lesion over her left cheek. A biopsy was performed and the subject reported the diagnosis as Bowen's disease (squamous cell carcinoma in situ). The study treatment was not discontinued due to the serious adverse event and it was reported as not resolved at the time of study completion.

Reviewer's Comment: With a history of previous malignant skin lesions, the diagnosis of Bowen's disease after approximately 4-6 weeks of mirabegron is not attributable to mirabegron, in my opinion.

Subject 3224-3015: Pregnancy: Subject is a 44 year old white Norwegian female randomized to mirabegron 50 mg [REDACTED] (b) (6). At the first visit on 2008-10-07, the pregnancy test was negative. The subject's approximate last menstruation period was on 2008-11-08 (day 11). The subject used condoms as a contraceptive. At the fourth visit on day 49, the subject reported pregnancy symptoms. A positive pregnancy test was determined by urine dipstick. The investigator considered this event as serious. On the same day (day 49), the study treatment was discontinued due to the serious adverse event of pregnancy. The subject had an elective abortion on day 73 which was reported as a serious adverse event. The serious adverse event of pregnancy was also reported as resolved on day 73.

Reviewer's Comment: Condoms are a medically approved and effective form of contraception. There was no protocol violation. This AE is not attributable to mirabegron. The event does serve as a reminder that young adult women do receive treatment for OAB. The risk to fetus due to mirabegron have been assessed by our PharmTox team as relatively remote, requiring a Pregnancy category C, not a Pregnancy category X.

Table 12: Treatment Emergent Adverse Events Leading to Discontinuation Study 178-CL-046

MedDRA (v9.1) System Organ Class Preferred Term <i>Table 19</i>	Placebo	Mirabegron		Tolterodine
	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Any Adverse Event	13 (2.6)	24 (4.9)	16 (3.2)	22 (4.4)
Gastrointestinal Disorders	4 (0.8)	5 (1.0)	4 (0.8)	5 (1.0)
Constipation	1 (0.2)	0	2 (0.4)	1 (0.2)
Gastritis	0	1 (0.2)	1 (0.2)	0
Abdominal Pain	0	1 (0.2)	0	1 (0.2)
Lip edema	0	1 (0.2)	0	0
Nausea	0	0	1 (0.2)	0
Vomiting	2 (0.4)	1 (0.2)	0	0
Abdominal Pain Lower	1 (0.2)	1 (0.2)	0	0
Abdominal Pain Upper	1 (0.2)	0	0	1 (0.2)
Diarrhea	0	0	0	1 (0.2)
Dry Mouth	0	0	0	1 (0.2)
Hemorrhoidal hemorrhage	0	0	0	1 (0.2)
Oral Soft Tissue Disorder	0	0	0	1 (0.2)
Cardiac Disorders	1 (0.2)	1 (0.8)	3 (0.6)	7 (0.7)
Tachycardia	0	1 (0.2)	1 (0.2)	0
Atrial Fibrillation	0	1 (0.2)	1 (0.2)	0
Angina Pectoris	0	1 (0.2)	0	0
Cardiac Failure Acute	0	0	1 (0.2)	0
Palpitations	0	0	1 (0.2)	1 (0.2)
Arrhythmia	0	0	0	1 (0.2)
Coronary Artery Disease	1 (0.2)	0	0	0
Sinus Tachycardia	0	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	0	3 (0.6)	3 (0.6)	1 (0.2)
Dermatitis Allergic	0	1 (0.2)	0	0
Hyperhidrosis	0	0	1 (0.2)	0
Pruritis Allergic	0	0	1 (0.2)	0
Skin Ulcers	0	0	1 (0.2)	0
Urticaria	0	1 (0.2)	0	0
Yellow Skin	0	1 (0.2)	0	0
Dry Skin	0	0	0	1 (0.2)
Rash Pruritic	0	0	0	1 (0.2)

MedDRA (v9.1) System Organ Class Preferred Term <i>Table 19 Continued</i>	Placebo	Mirabegron		Tolterodine
	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
General Disorders and Administrative Site Conditions	4 (0.8)	2 (0.4)	3 (0.6)	3 (0.6)
Edema Peripheral	1 (0.2)	1 (0.2)	1 (0.2)	0
Asthenia	0	0	1 (0.2)	0
Edema	0	1 (0.2)	0	0
Pyrexia	0	0	1 (0.2)	0
Chest Pain	2 (0.4)	0	0	0
Fatigue	0	0	0	3 (0.6)
Local Swelling	1 (0.2)	0	0	0
Nervous System Disorders	0	3 (0.6)	1 (0.2)	5 (1.0)
Headache	0	1 (0.2)	1 (0.2)	2 (0.4)
Dizziness	0	1 (0.2)	0	1 (0.2)
Somnolence	0	1 (0.2)	0	0
Dysgeusia	0	0	0	1 (0.2)
Epilepsy	0	0	0	1 (0.2)
Vascular Disorders	1 (0.2)	3 (0.6)	0	2 (0.4)
Hypertensive Crisis	0	2 (0.4)	0	0
Arteriosclerosis	0	1 (0.2)	0	0
Hypertension	1 (0.2)	0	0	1 (0.2)
Hypotension	0	0	0	1 (0.2)
Immune System Disorders	0	1 (0.2)	1 (0.2)	1 (0.2)
Drug Hypersensitivity	0	0	1 (0.2)	0
Hypersensitivity	0	1 (0.2)	0	1 (0.2)
Investigations	0	2 (0.4)	0	0
Blood Pressure Decreased	0	1 (0.2)	0	0
Hepatic Enzyme Increased	0	1 (0.2)	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	0	02 (0.4)	1 (0.2)
Myalgia	0	0	1 (0.2)	0
Osteoarthritis	0	0	1 (0.2)	0
Arthralgia	0	0	0	1 (0.2)
Back Pain	1 (0.2)	0	0	0
Renal and Urinary Disorders	1 (0.2)	2 (0.4)	0	3 (0.6)
Nephrolithiasis	0	1 (0.2)	0	0
Urinary Retention	0	1 (0.2)	0	3 (0.6)
Hypertonic Bladder	1 (0.2)	0	0	0

MedDRA (v9.1) System Organ Class Preferred Term <i>Table 19 Continued</i>	Placebo	Mirabegron		Tolterodine
	(n=494)	50 mg (n=493)	100 mg (n=496)	SR 4 mg (n=495)
	n (%)			
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.2)	1 (0.2)	0
Dyspnea	0	1 (0.2)	1 (0.2)	0
Ear and Labyrinth Disorders	0	1 (0.2)	0	1 (0.2)
Ménière's Disease	0	1 (0.2)	0	0
Vertigo	0	0	0	1 (0.2)
Eye Disorders	0	1 (0.2)	0	1 (0.2)
Open Angle Glaucoma	0	1 (0.2)	0	0
Dry Eye	0	0	0	1 (0.2)
Infections and Infestations	2 (0.4)	1 (0.2)	0	2 (0.4)
Postoperative Infection	0	1 (0.2)	0	0
Cystitis	0	0	0	1 (0.2)
Influenza	0	0	0	1 (0.2)
Viral Infection	2 (0.4)	0	0	0
Pregnancy, Puerperium and Perinatal Conditions	0	1 (0.2)	0	0
Pregnancy	0	1 (0.2)	0	0
Psychiatric Disorders	1 (0.2)	0	1 (0.2)	0
Anxiety Disorder	0	0	1 (0.2)	0
Anxiety	1 (0.2)	0	0	0
Insomnia	0	0	0	1 (0.2)
Reproductive System and Breast Disorders	0	1 (0.2)	0	0
Breast Engorgement	0	1 (0.2)	0	0
Injury, Poisoning and Procedural Complications	0	0	0	2 (0.4)
Fall	0	0	0	1 (0.2)
Road Traffic Accident	0	0	0	1 (0.2)

Source: Table 38, Study 178-CL-046, page 137

Reviewer's comment: In this study, only two AEs leading to discontinuation were reported by more than 1 patient; these were constipation (n=2) and hypertensive crisis (n=2).

Selected narratives in brief excluding those cases discussed in SAEs.

Subject 3118-1489: Abdominal Pain: Somnolence: Blood Pressure Decreased: The subject is a 54 year old white Polish female randomized to mirabegron 50 mg on 4 August 2008. The subject received a total of 47 days of study drug. The study treatment was discontinued due to the adverse events of abdominal pain, decreased blood pressure, and drowsiness on Day 47 (2008-09-19). No medical history is included in narrative and no concomitant medications were reported.

On Day 30, subject experienced the adverse events of abdominal pain and drowsiness. On the same Day, the subject experienced an adverse event of decreased blood pressure (blood pressure data not provided in narrative or CRF). The subject did experience episodes of hypotension prior to study drug administration with Day -6 values of 98/65 and 98/68 mm Hg and with day -5 values of 85/61. The study drug therapy was discontinued due to the adverse events of abdominal pain, drowsiness and decreased blood pressure on Day 47. The adverse event of abdominal pain and drowsiness resolved on Day 51 and the adverse event of decreased blood pressure resolved on Day 52 (blood pressures not provided).

Reviewer's Comment: The patient had documented low blood pressure prior to mirabegron exposure. Based on a positive dechallenge, however, a relationship between abdominal pain and drowsiness and mirabegron cannot be excluded. The case also lacks details on the actual blood pressures. In the absence of blood pressure data, I cannot attribute low blood pressure to mirabegron.

Subject 3281-1373: Tachycardia: Dyspnea: The subject is a 62 year old white Italian male randomized to mirabegron 50 mg 26 July 2008. The subject received a total of 51 days of study drug. Study treatment was discontinued due to the adverse events of dyspnea (difficulty breathing) and tachycardia on day 51. The medical history included plastic surgery for inguinal hernia (1988) and overactive bladder (since 2001). There were no concomitant medications.

On Day 31 the subject reported adverse events of tachycardia and dyspnea. Vital signs recordings for Day 31 were not available. The subject showed abnormal ECG results on Day 52. Average vital signs and ECG findings are shown in Tables 1 and 2, respectively. Study drug was discontinued due to the events of tachycardia and dyspnea on Day 51. The event of tachycardia was reported resolved on Day 52 and the event of dyspnea was reported as resolved on Day 53.

Subject 3281-1373 ECG Findings:

Day	HR Mean (bpm)	PR Mean (msec)	QRS Duration (msec)	RR Mean (msec)	QTCF Mean (msec)	QTCB Mean (msec)	QT Mean (msec)	Overall ECG Interpretation
-15	48	257	83	1251	409	394	441	Abnormal: First degree AV block; sinus bradycardia
52	52	239	89	1165	419	409	441	Abnormal: First degree AV block

Source: Patient Narrative Subject 3281-1373

Vital Signs:

Clinical Review
 {Insert Reviewer Name}
 {Insert Application Type and Number}
 {Insert Product Trade and Generic Name}

Visit or Day/Device	BP (mmHg)	Heart Rate (bpm)
Baseline: Home Device	142/81	51
Baseline: Office Device	120/80	53
Week 8: Home Device	137/70	54
Week 8: Office Device	120/78	56

Source: Patient Narrative Subject 3281-1373

Reviewer’s Comment: It is notable that an AE of tachycardia was reported, but the patient’s heart rate by ECG on the day of the report was 52 beats per minute, up from 48 beats per minute on screening ECG. Other than “difficulty breathing”, there is no description of the patient’s dyspnea. The vital signs for Day 31 (the day of tachycardia) documenting tachycardia are not available. In this poorly documented event, in the absence of alternative explanations, a causal association of these events and mirabegron cannot be excluded but analysis is confounded.

Subject 3011-1858: Tachycardia: Asthenia: The subject is a 74 year old white German female randomized to 100 mg of mirabegron 2 September 2008. The subject received a total of 23 days of study drug. The study treatment was discontinued due to the adverse events of tachycardia and weakness on day 23 (2008-09-24). The medical history included hypertension (since 1980), estrogen deficiency (since 1999), hysterectomy (1999), osteoporosis (since 2000), varicose vein operation right (2004). Concomitant medications include nebivolol, vaginal estrogen (estriol), triamterene and intra-articular etoricoxib.

On Day 18 and Day 22, the subject experienced adverse events of tachycardia and weakness, respectively. The subject had a history of hypertension and was taking triamterene orally 1 tablet daily, since 2001, as well as nebivolol. The study treatment was discontinued due to the events of tachycardia and weakness on day 23. No information regarding pulse rate or physical exam findings during this period were available. The events of tachycardia and weakness were reported as resolved on day 29. The ECG findings are below:

Day	HR Mean (bpm)	PR Mean (ms)	QRS Duration (ms)	RR Mean (ms)	QTCF Mean (ms)	QTCB Mean (ms)	QT Mean (ms)	ECG Interpretation	Comments
-21	74	235	84	807	481	498	448	ABNORMAL	First Degree AV Block
58	58	221	93	1042	461	458	467	ABNORMAL	First Degree AV Block

Source: Patient Narrative 3011-1858.

Reviewer’s Comment: Nebivolol is a beta-1 blocker. Mirabegron is a non selective beta-3 agonist (Study 178-CL-053). It is possible that mirabegron played some role in the AE of tachycardia, but in this case, the actual heart rate cannot be determined and the clinical sequelae, if any, were unspecified.

Subject 3195-1620: Palpitations: Hyperthyroidism The subject is a 28 year old white Finish female randomized to mirabegron 100 mg on 13 August 2008. The subject received study drug for a total of 27 days. The study treatment was discontinued on day 27 due to the adverse event of palpitations (reported as: palpitation that also recorded by a pulse 92-102 constantly (at baseline 66-73)). There is no past medical history included in the narrative. The patient utilized drospirenone/ethinyl estradiol for birth control starting Day -12.

On Day 16, the subject experienced an adverse event of palpitations. The study treatment was discontinued on Day 27 due to the adverse event of palpitations. On Day -15, the subject's ECG showed mean heart rate of 85 BPM, mean PR interval 177 ms, mean RR interval 704 ms, mean QRS complex duration 86 ms and mean QT interval 337 ms. On Day 28, the subject's ECG showed mean heart rate of 87 BPM, mean PR interval 164 ms, mean RR interval 693 ms, mean QRS complex duration 88 ms and mean QT interval 340 ms. The subject's pulse rates were still in the range of 92-102 on Day 29 (last recording) and the event was considered not resolved at the time of study completion. Physical examination of the subject on day 29 indicated palpitations and the results were reported as changed but not clinically significant.

On Day 54, the subject experienced an adverse event of hyperthyroidism. The subject started carbimazole orally for a total daily dose of 5 mg since Day 54. The subject did not recover and the adverse event of hyperthyroidism was reported as not resolved at the time of study completion.

Reviewer's Comment: The palpitations could be causally related to mirabegron but they could also be related to new-onset hyperthyroidism. The evaluation of mean, shift, and PCS data for thyroid analytes collected during study 178-CL-074 did not suggest differences across total mirabegron, placebo, and tolterodine treatment groups. It is unlikely that mirabegron use resulted in the AE of hyperthyroidism. Palpitations and its possible association with mirabegron is better assessed in the aggregate safety summary.

Reviewer's Comment: The SOCs of Cardiac Disorders(atrial fibrillation, tachycardia [1 each in 50 mg mirabegron group versus 0 for placebo]) Nervous System(headache, dizziness and somnolence [1 each in 50 mg mirabegron 100 mg mirabegron groups versus 0 for placebo group] and Vascular(hypertensive crisis [2]) have 1 case each for mirabegron 50 mg versus placebo. The 2 cases of hypertensive crisis in my opinion were exacerbations of pre-existing hypertension. Pruritis allergic (1 in a 100 mirabegron pt) and dermatitis allergic (1 in a mirabegron 50 mg patient) were also reported.

Clinical Laboratory Hematology:

Mean changes from baseline to each visit in hematology variables were similar across the treatment groups. No trends in the change from baseline were observed between the mirabegron and placebo or tolterodine SR 4 mg groups in these parameters. Patient 1639, on mirabegron 50 mg, was noted to a platelet count of $137 \times 10^9/L$ at baseline and $111 \times 10^9/L$ at study completion.

Mirabegron 50 mg patients 1429 and 2659 had normal baseline platelets (158 and 218 x 10⁹/L at baseline respectively) and at study end had platelets of 118 and 104 x 10⁹/L respectively. There was no such finding in placebo or mirabegron 100 subjects. One mirabegron 100 mg patient had low platelet count of 124 x 10⁹/L at study end (2537) which was preceded by a platelet count of 118 x 10⁹/L (baseline 157 x 10⁹/L). Tolterodine had no patient with a low platelet count at endpoint.

Clinical Laboratory: Serum Chemistry

Mean changes from baseline to each visit in serum chemistry variables were similar across the treatment groups; mean changes from baseline in all analytes were of small magnitude compared to the normal range of the analyte. No trends in the change from baseline were observed between the mirabegron and placebo or tolterodine SR 4 mg groups in these parameters. No differences were observed among the treatment groups in shifts from baseline to the most extreme value during the treatment period.

No patient had a serum creatinine value that met the PCS criterion. The incidence of patients whose blood urea nitrogen value met the PCS (potentially clinically significant) criterion was 0.8% (4/482), 0.6% (3/478), 0.2% (1/479), and 0.4% (2/480) in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively. Of the three mirabegron 50 mg patients who met the PCS BUN criteria: 2 had hypertension and 1 had cardiac disease. All three had BUN elevations prior to mirabegron exposure.

No patients met laboratory criteria for Hy's Law (i.e., concomitant elevations in ALT and/or AST > 3 X ULN and total bilirubin > 2 X ULN). No patient in the 50 mg mirabegron group had an AST elevation >3 x ULN. No patient in the 50 mg mirabegron group had an AST elevation > 3 x ULN. Elevations meeting the potentially clinically significant (PCS) criteria for ALT, AST, ALP, bilirubin and/or GGT were observed in patients in all treatment groups. The overall incidence of hepatic TEAEs was 1.4% (7/494) in the placebo group, 2.2% (11/493) in the mirabegron 50 mg group, 1.4% (7/496) in the mirabegron 100 mg group, and 2.0% (10/495) in the tolterodine SR 4 mg group. The incidence of mild TEAEs was comparable among placebo-treated (1.2%), mirabegron-treated (1.3%), and tolterodine SR 4 mg-treated (1.2%) patients. The incidence of moderate TEAEs was 0.2% in the placebo group, 0.5% in the combined mirabegron groups, and 0.8% in the tolterodine SR 4 mg group. There were no severe hepatic treatment-emergent TEAEs. Treatment-emergent hepatic SAEs were reported by 1 patient (Patient No. 3312-3435 Narrative in SAE section) in the mirabegron 50 mg group (hepatic enzyme increased, PT) and 1 patient in the tolterodine SR 4 mg group (hepatitis, PT). Permanent discontinuation of study drug due to a hepatic TEAE occurred in 2 patients: Patient No. 3374-3435 in the mirabegron 50 mg group permanently discontinued study drug due to the SAE of hepatic enzyme increased (PT) and Patient No. 3374-3234 permanently discontinued study drug (mirabegron 50 mg) due to a TEAE of yellow skin (PT). At no time were hepatic enzymes elevated in this patient. At the time of discontinuation, this patient's bilirubin was 10 umol/L.

Table 4: Increased Liver Chemistry Values Study 178-CL-046

Laboratory	Placebo	Mirabegron		Tolterodine
Parameter		50 mg	100 mg	SR 4 mg
Increased	n=494	n=493	n=496	n=495
	n(%)			
ALT	2 (0.4)	5 (1.0)	3 (0.6)	4 (0.8)
AST	0	2 (0.4)	3 (0.6)	3 (0.6)
GGT	3 (0.6)	2 (0.4)	3 (0.6)	3 (0.6)
Bili	0	2 (0.4)	0	0
Hepatic Enzyme	0	1 (0.2)	1 (0.2)	1 (0.2)
Liver Function Test Abnormal	1 (0.2)	0	1 (0.2)	1 (0.2)
AP	0	0	0	2 (0.4)
Transaminases Increased	0	1 (0.2)	0	0
GGT>100 U/L	11/482 (2.3%)	8/478 (1.7%)	16/479 (3.3%)	18/480 (3.8%)

ALT=alanine aminotransferase, AST=Aspartate aminotransferase, AP=Alkaline Phosphatase, Bili=Bilirubin, GGT=Gamma glutamyl transferase

Source: Table 50, Study Report 178-CL-046, page 172.

The mean change from baseline to each visit and to the Final Visit in the hemoglobin A1c fraction was comparable across all treatment groups. Although there were slight increases in the incidence of patients whose HbA1c value met the PCS criterion in the mirabegron groups, overall abnormalities and change from baseline in HbA1c was comparable across all treatment groups.

Reviewer's Comment: The overall incidence of hepatic TEAEs was 1.4% in placebo, 2.2% in mirabegron 50 mg and 1.4% in mirabegron 100 mg patients. All TEAEs were mild or moderate intensity in all treatment groups. This does not, in my opinion, generate a safety concern.

Vital Signs

Based on the ANCOVA model on the overall population, the adjusted mean change from baseline to Final Visit in AM pulse rate was 0.8 bpm in the placebo group, 1.6 bpm in the mirabegron 50 mg group, 2.4 bpm in the mirabegron 100 mg group and 1.6 bpm in the tolterodine SR 4 mg group. The adjusted mean difference versus placebo in AM pulse rate at the Final Visit was 0.8 and 1.6 bpm for the mirabegron 50 mg and 100 mg groups and 0.8 bpm for the tolterodine SR 4 mg group. The adjusted mean change from baseline to week 4 in PM pulse

rate of -0.5, 0.7, 2.3, and 2.2 bpm was observed in patients in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively.

In the normotensive population, the adjusted mean differences versus placebo in AM and PM pulse rates at the Final Visit were 0.6 and 0.8 bpm for the mirabegron 50 mg group, 1.3 and 2.2 bpm for the mirabegron 100 mg group and 0.5 and 2.1 bpm for the tolterodine SR 4 mg group. In the hypertensive population, the adjusted mean differences versus placebo in AM and PM pulse rates at the Final Visit were 0.9 and 0.3 bpm for the mirabegron 50 mg group, 2.1 and 1.5 bpm for the mirabegron 100 mg group and 1.3 and 1.6 bpm for the tolterodine SR 4 mg group.

Dose-dependent increases in AM and PM pulse rate were observed in female patients (0.8 and 2.6 bpm for 50 and 100 mg mirabegron respectively) in the mirabegron groups; male patients treated with mirabegron did not demonstrate dose dependent changes (0.8 and 0.6 bpm for 50 and 100 mg mirabegron respectively). Females treated with mirabegron 100 mg had a higher adjusted mean increase from placebo than males for AM and PM pulse rates. Dose-dependent increases in AM and PM pulse rate were observed in patients < 65 (0.8 and 2.2 bpm for 50 and 100 mg mirabegron respectively) and ≥65 years of age (0.4 and 1.5 bpm for 50 and 100 mg mirabegron respectively). In the mirabegron groups, the adjusted mean increase from placebo in AM pulse rate was greater in patients ≥ 65 years of age than in patients < 65 years of age; the opposite was observed for PM pulse rates. Additionally, dose-dependent increases in AM and PM pulse rate were observed in patients < 75 years of age and in patients ≥75 years of age. The adjusted mean difference from placebo in AM and PM pulse rate was higher in patients ≥ 75 years of age compared to patients < 75 years of age.

In the overall population and the hypertensive population, the mean difference versus placebo at the Final Visit in AM and PM systolic blood pressure (SBP) and diastolic blood pressure (DBP) was similar across the treatment groups. There was a numeric increase of generally less than 1.5 mm Hg in the mean change from baseline in the mirabegron groups by central tendency analysis. The Sponsor concludes that cases of new hypertension occurred but with equal frequency in the placebo group and would be expected in this population. Finally, there was no “at risk” subgroup for blood pressure increases on treatment either by demographics or when divided up by history of hypertension, active hypertension, or no history of hypertension.

The Sponsor conducted outlier analysis regarding the following categories:

Table 5: AM Systolic Blood Pressure Outliers Study 178-CL-046

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=494	n=493	n=496
Final Visit	AM Systolic		Exceeded Placebo	Yes/No
Change from Baseline ≥15 mmHg		26/482 (5.4)	Yes (5.9)	Yes (5.6)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥10 mmHg		14/449 (3.1)	No	No
Change from Baseline ≥15 mmHg		5/449 (1.1)	No	No

Change from Baseline ≥ 20 mmHg		4/449 (0.9)	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		40/464 (8.6)	No	No
Change from Baseline ≥ 15 mmHg		16/464 (3.4)	No	No
Change from Baseline ≥ 20 mmHg		8/464 (1.7)	No	No
Normotensive Pop		n=298	n=321	n=313
Final Visit	AM Systolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 15 mmHg		12/288 (4.2)	Yes (4.8)	Yes (6.3)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		5/270 (1.9)	Yes (2.4)	Yes (3.3)
Change from Baseline ≥ 15 mmHg		1/270 (0.4)	No	Yes (1.8)
Change from Baseline ≥ 20 mmHg		1/270 (0.4)	No	Yes (1.1)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		21/276 (7.6)	No	Yes (7.7)
Change from Baseline ≥ 15 mmHg		6/276 (2.2)	No	Yes (2.8)
Change from Baseline ≥ 20 mmHg		2/276 (0.7)	Yes (1.0)	Yes (1.4)
Hypertensive Pop		n=196	n=172	n=183
Final Visit	AM Systolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 15 mmHg		14/193 (7.3)	Yes (8.0)	No
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		9/179 (5.0)	No	No
Change from Baseline ≥ 15 mmHg		4/179 (2.2)	No	No
Change from Baseline ≥ 20 mmHg		3/179 (1.7)	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		19/188 (10.1)	No	No
Change from Baseline ≥ 15 mmHg		10/188 (5.3)	No	No
Change from Baseline ≥ 20 mmHg		6/188 (3.2)	No	No

Source: Table 70: Study Report 178-CL-046, page 203.

Table 6: PM Systolic Blood Pressures Outliers Study 178-CL-046

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=494	n=493	n=496
Final Visit	PM Systolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 15 mmHg		34/479 (7.1%)	No	Yes (7.7%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		11/447 (2.5%)	Yes (4.1%)	Yes (4.8%)
Change from Baseline ≥ 15 mmHg		2/447 (0.4%)	Yes (1.1%)	Yes (1.6%)
Change from Baseline ≥ 20 mmHg		1/447 (0.2%)	No	Yes (0.7%)
2 Consecutive Postbaseline Visits				

Change from Baseline ≥ 10 mmHg		36/462 (7.8%)	Yes (8.4%)	Yes (10.1%)
Change from Baseline ≥ 15 mmHg		8/462 (1.7%)	Yes (2.0%)	Yes (3.5%)
Change from Baseline ≥ 20 mmHg		2/462 (0.4%)	Yes (1.1%)	Yes (1.8%)
Normotensive Pop		n=298	n=321	n=313
Final Visit	PM Systolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 15 mmHg		16/288 (5.6%)	No	Yes (7.0%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		2/270 (0.7%)	Yes (3.8%)	Yes (3.8%)
Change from Baseline ≥ 15 mmHg		0	Yes (1.4%)	Yes (1.4%)
Change from Baseline ≥ 20 mmHg		0	Yes (0.3%)	Yes (0.3%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		15/276 (5.4%)	Yes (8.8%)	Yes (11.2%)
Change from Baseline ≥ 15 mmHg		1/276 (0.4%)	Yes (2.4%)	Yes (3.2%)
Change from Baseline ≥ 20 mmHg		0	Yes (1.4%)	Yes (1.8%)
Hypertensive Pop		n=196	n=172	n=183
Final Visit	PM Systolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 15 mmHg		18/191 (9.4%)	No	No
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		9/177 (5.1%)	No	No
Change from Baseline ≥ 15 mmHg		2/177 (1.1%)	No	Yes (2.4%)
Change from Baseline ≥ 20 mmHg		1/177 (0.6%)	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		21/186 (11.3%)	No	No
Change from Baseline ≥ 15 mmHg		7/186 (3.8%)	No	No
Change from Baseline ≥ 20 mmHg		2/186 (1.1%)	No	Yes (1.8)

Source: Table 70, Study 178-CL-046, page 204

Reviewer's Comment: In normotensive patients, mirabegron 50 mg appears to have a modestly increased incidence of systolic blood pressure outliers in the PM systolic group compared to placebo. It should be noted that the values for AM and PM vital sign measurements at each of the specified visits was calculated by averaging 6 measurements (the last 2 of 3 measurements from the last 3 of 5 days prior to the protocol visit. This help to dampen out the variability in some patients' vital signs. Based on the known dose-response for blood pressure observed in Phase 1 studies, the recommended starting dose of 25 mg will have even less blood pressure effects.

Table 7: AM Diastolic Blood Pressure Outliers Study 178-CL-046

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=494	n=493	n=496
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		21/481 (4.4%)	Yes (5.5%)	Yes (4.8%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		29/449 (6.5%)	No	Yes (7.7%)
Change from Baseline \geq 15 mmHg		5/449 (1.1%)	No	Yes (1.6%)
Change from Baseline \geq 20 mmHg		0	No	Yes (0.5%)
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		65/464 (14.0%)	Yes (14.4%)	Yes (15.4%)
Change from Baseline \geq 15 mmHg		14/464 (3.0%)	No	No (2.6%)
Change from Baseline \geq 20 mmHg		2/464 (0.4%)	No	Yes (0.7%)
Normotensive Pop		n=298	n=321	n=313
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10mmHg		13/288 (4.5%)	Yes (6.1%)	Yes (6.3%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		17/270 (6.3%)	No	Yes (8.7%)
Change from Baseline \geq 10 mmHg		3/270 (1.1%)	No	Yes (2.2%)
Change from Baseline \geq 15 mmHg		0	No	Yes (0.7%)
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		37/276 (13.4%)	Yes (16.9%)	Yes (15.8%)
Change from Baseline \geq 10 mmHg		8/276 (2.9%)	No	Yes (3.2%)
Change from Baseline \geq 15 mmHg		1/276 (0.4%)	No	Yes (1.1%)
Hypertensive Pop		n=196	n=172	n=183
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		8/193 (4.1%)	Yes (4.3%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		12/179 (6.7%)	No	No
Change from Baseline \geq 10 mmHg		2/179 (1.1%)	Yes (1.3%)	No
Change from Baseline \geq 15 mmHg		0	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		28/188 (14.9%)	No	No
Change from Baseline \geq 10mmHg		6/188 (3.2%)	No	No
Change from Baseline \geq 15 mmHg		1/188 (0.5%)	No	no

Source: Table 71, Study 178-CL-046

Table 8: PM Diastolic Blood Pressure Outliers Study 178-CL-046

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=494	n=493	n=496
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 10 mmHg		23/479 (4.8%)	Yes (6.1%)	Yes (8.4%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		20/447 (4.5%)	Yes (4.8%)	Yes (4.8%)
Change from Baseline ≥ 10 mmHg		3/447 (0.7%)	No	No
Change from Baseline ≥ 15 mmHg		0	Yes (4.8%)	Yes (4.8%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		51/462 (11.0%)	Yes (15.1%)	Yes (20.7%)
Change from Baseline ≥ 10 mmHg		8/462 (1.7%)	Yes (2.0%)	Yes (4.0%)
Change from Baseline ≥ 15 mmHg		0	No	Yes (0.9%)
Normotensive Pop		n=298	n=321	n=313
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 10 mmHg		14/288 (4.9%)	Yes (6.7%)	Yes (9.3%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		11/270 (4.1%)	Yes (5.2%)	Yes (10.5%)
Change from Baseline ≥ 10 mmHg		0	No	Yes (1.8%)
Change from Baseline ≥ 15 mmHg		11/270 (4.1%)	Yes (5.2%)	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		30/276 (10.9%)	Yes (18.2%)	Yes (21.4%)
Change from Baseline ≥ 10 mmHg		3/276 (1.1%)	Yes (2.0%)	Yes (4.2%)
Change from Baseline ≥ 15 mmHg		0	No	Yes (1.1%)
Hypertensive Pop		n=196	n=172	n=183
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline ≥ 10 mmHg		9/191 (4.7%)	Yes (4.9%)	Yes (6.8%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		9/177 (5.1%)	No	Yes (7.2%)
Change from Baseline ≥ 10 mmHg		3/177 (1.7%)	No	No
Change from Baseline ≥ 15 mmHg		0	Yes (4.0%)	Yes
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg		21/186 (11.3%)	No (9.1%)	Yes (19.4%)
Change from Baseline ≥ 10 mmHg		5/186 (2.7%)	No	Yes (3.5%)
Change from Baseline ≥ 15 mmHg		0	No	Yes (0.6%)

Source: Table 72, Study 178-CL-046 Report, page 206

Reviewer's Comment: There appears to be modest increase in diastolic PM outliers in the normotensive 50 mg subject group. This along with similar findings in the

normotensive PM systolic outliers may suggest a tendency for mirabegron 50 mg to modestly increase the blood pressure outliers in normotensive individuals in this study. This possible tendency will be assessed in the other studies and in aggregate analysis. Additionally, the reader should be aware that the blood pressure effect in Phase 1 studies is dose-related and the recommended starting dose in all patients will be 25 mg.

ECGs

Mean changes from baseline to the Final Visit in ECG parameters were similar across all treatment groups for all parameters except the mean RR interval, which was consistent with the effect on pulse rate.

Table 9: Changes from Baseline to Final Visit in Heart Rate and QTcF Interval Study 178-CL-046

Parameter	Placebo n=494	Mirabegron 50 mg n=493	Mirabegron 100 mg n=496
Heart Rate (bpm)			
n at Baseline	467	470	471
Baseline Mean (SD)	68.1 (10.67)	68.1 (11.18)	67.6 (10.85)
n at Final Visit	426	419	428
Baseline Δ Final Visit	1.7 (9.61)	1.7 (9.81)	2.8 (9.36)
QTcF (msec)			
n at Baseline	467	469	471
Baseline Mean (SD)	401.8 (23.67)	402.0 (23.11)	401.8 (22.98)
n at Final Visit	425	418	428
Baseline Δ Final Visit	-2.8 (19.25)	-0.7 (19.17)	-1.3 (19.89)

Source: Table 77, 178-CL-046 Study Report, page 212

QTcF absolute values > 500 msec at the Final Visit were observed for 1 (0.2%) patient in the mirabegron 100 mg group and 1 (0.2%) patient in the tolterodine SR 4 mg group.

Neither of these patients had a TEAE of QTc interval prolongation reported. A ≥ 60 msec change from baseline in QTcF was observed for 1 patient in the placebo group, 1 patient in the mirabegron 50 mg group, 2 patients in the mirabegron 100 mg group, and 2 patients in the tolterodine SR 4 mg group.

With few exceptions, the overall incidence of any finding within each category was similar across all treatment groups. The exceptions included the categories (abnormality) low grade AV block (first degree AV block) and ECG changes consistent with myocardial infarction (all abnormalities). The incidence of first degree AV block was 1.6% (7/494) in the placebo group, 1.9% (8/493) in the mirabegron 50 mg group, 5.2% (23/496) in the mirabegron 100 mg group and 0.2% (1/495) in the tolterodine SR 4 mg group. Two (0.5%) patients in the tolterodine SR 4

mg group had changes consistent with prior myocardial infarction; no patients in any other treatment group had ECG changes consistent with myocardial infarction.

Treatment-emergent prolonged QTc interval, defined by the central reader as mean QTcB or QTcF > 499 msec, was noted in 4 patients (1 in the mirabegron 100 mg group and 3 in the tolterodine SR 4 mg group) during the double-blind period. Treatment-emergent sinus tachycardia, defined by the central reader as mean HR > 100 bpm and mean PR not null, was reported for 5 (1.1%), 5 (1.2%), 2 (0.4%) and 12 (2.8%) in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively.

Mean increases from baseline to Final Visit in heart rate were numerically higher for male patients than female patients in the mirabegron 50 mg group, but were comparable in male and female patients across all other treatment groups. No consistent changes in mean change from baseline to Final Visit in QTcF were observed in male or female patients. Mean increases from baseline to Final Visit in heart rate were similar for patients < 65 years of age and ≥ 65 years of age across all treatment groups. No consistent changes from baseline to Final Visit in QTcF were observed in patients < 65 years of age and ≥ 65 years of age.

Reviewer's Comment: In general, in this study, heart rate changes observed on ECGs are very modest and virtually nil for the maximum recommended dose of 50 mg. No consistent ECG trends were identified. In addition, no sequelae of QT interval prolongation such as ventricular tachycardia, ventricular fibrillation or torsades de pointes were noted. QTcF absolute values >500 msec were observed in 1 patient in the mirabegron 100 mg group and 1 patient in the tolterodine SR 4 mg group; the patient in the mirabegron 100 mg group had a baseline QTcF of 495 msec.

Post Void Residual Volume

No patients in any treatment group had a PVR > 500 mL during the study. The mean change from baseline to Final Visit in PVR was -2.4, -1.3, 0.3, and -0.5 mL in the placebo, mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg groups, respectively.

Reviewer's Summary

In this study, the efficacy of mirabegron at doses of 50 and 100 mg once daily for 12 weeks was demonstrated for each of the symptoms of the OAB syndrome, including micturition frequency, incontinence episodes, and volume voided, and their effect on QoL. Both doses of mirabegron were effective in treating these symptoms of OAB at week 4 (the first postdose assessment period) and efficacy was maintained throughout the 12-week treatment period.

Mirabegron in both the 50 mg and 100 mg doses reduced incontinence episodes in patients which is a clinically meaningful improvement.

A significant treatment by age interaction (age group < 65 and ≥ 65 years of age) was observed, with increased efficacy in the elderly population for the mean number of incontinence episodes while a significant treatment by sex interaction was observed for mean number of micturition episodes (better in females). The study was not powered for these analyses, and definitive conclusions cannot be drawn. Treatment with mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg resulted in a statistically significant increase compared to placebo in the mean volume voided per micturition at the Final Visit (adjusted mean difference from placebo: 11.9 mL, 13.2 mL and 12.6 mL, respectively). Both doses of mirabegron by Week 4 also demonstrated a statistically significant reduction compared to placebo in the mean number of incontinence episodes per 24 hours (-0.39 for mirabegron 50 mg and -0.38 for mirabegron 100 mg).

Although in this study tolterodine demonstrated a benefit, the magnitude of that benefit was smaller than expected, and may have been influenced by the design features of this study, including the inclusion criteria for incontinence as described above as well as the fact that the population examined in this study included patients that may have been previously treated with anticholinergics who discontinued due to limited efficacy.

Overall, 43.2% of all patients experienced 1 or more TEAEs during the study. One death occurred in a patient treated with tolterodine.

The adverse events reported at greater frequency in the mirabegron 50 mg group compared to placebo were headache and nasopharyngitis, and even these were only reported at a modestly greater frequency in the drug compared to placebo group. The overall incidence of hypertension was similar across treatment groups. In my own analysis (see in Reviewers Comment beneath TEAEs Summary table), it does not appear that treatment emergent hypertension is related to mirabegron use. In this study, investigators were provided pre-specified definitions for reporting of hypertension AEs, which may have led to a relatively greater incidence of AEs reported as “hypertension” compared to results observed in the phase 2 dose-finding studies which did not include these prespecified definitions. Events of cardiac arrhythmia were treatment limiting in 3 patients in each of the active-treatment groups (mirabegron 50 mg, mirabegron 100 mg and tolterodine SR 4 mg); none of the placebo-treated patients with cardiac arrhythmia events discontinued study drug due to the event. Tachycardia was noted in 2 mirabegron 50 mg subjects and 1 mirabegron 100 mg subject as a cause for discontinuation. Tachycardia reported as an AE occurred in 2 placebo subjects, 4 mirabegron 50 mg subjects and 1 mirabegron 100 mg subject. Based upon criteria that were employed to identify medically important cases of atrial fibrillation, treatment-emergent atrial fibrillation was observed in 1 placebo-treated patient, 2 patients in each mirabegron group and 5 patients treated with tolterodine SR 4 mg. In all but one of the atrial fibrillation cases, alternative etiologies were discerned for the atrial fibrillation events. The overall incidence of adjudicated cardiovascular events (both ischemic and non-ischemic) was comparable in placebo-treated (0.2%) and mirabegron-treated patients (total incidence [50mg and 100mg combined], 0.4%) and slightly higher in tolterodine-treated patients (0.6%). No episodes of syncope were reported in this study.

The incidence of TEAEs indicative of hypersensitivity was similar across treatment groups.

No patient met the laboratory criteria for Hy's Law (i.e., concomitant elevations in ALT and/or AST > 3 times the ULN and total bilirubin > 2 times the ULN). The overall incidence of hepatic disorders events in the Possible Drug related Hepatic Disorders SMQ was 1.4%, 2.2%, 1.4% and 2.0% in the placebo, mirabegron 50 mg mirabegron 100 mg, and tolterodine SR 4 mg groups, respectively. All hepatic TEAEs were mild or moderate in intensity and were rarely treatment limiting; 2 patients in the mirabegron 50 mg group discontinued study drug due to hepatic events. There was no obvious effect of mirabegron on increasing hepatic enzymes in this study.

A dose-dependent increase in pulse rate (difference from placebo) of 0.8 and 1.6 bpm (AM measures) and 0.7 and 2.0 bpm (PM measures) was observed for the mirabegron 50 and 100 mg groups. Study drug was discontinued due to an event related to increased heart rate in 0, 2, 1, and 1 patients in the placebo, mirabegron 50 mg, mirabegron 100 and tolterodine SR 4 mg groups, respectively. Analyses of vital signs by subgroup populations showed a slightly higher increase in pulse rate in females compared to males in mirabegron-treated patients.

The adjusted mean change of the blood pressure in this study was -0.1 mmHg for mirabegron 50 mg and 0.3 mmHg for mirabegron 100 mg (Table 14, Cardiovascular Research Report, page 54). There may have been a slight trend for increased BP outliers in PM systolic and diastolic BP in the mirabegron groups compared to placebo. No consistent ECG trends were identified.

Overall: Mirabegron, based on this study, is safe to use for the intended indication and has a favorable risk/benefit for use. The data from this support the safety and efficacy of mirabegron, especially at the to-be-marketed 25 mg to 50 mg dose-titration regimen.

Study 178-CL-047 (Aries): A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects with Symptoms of Overactive Bladder

This multinational, multicenter study was conducted at 132 sites in the United States (115 sites) and Canada (17 sites). A total of 141 sites were initiated; 132 sites enrolled patients.

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

This was a randomized, parallel group, placebo-controlled, double-blind, multinational, multicenter study conducted in patients with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) of at least 3 month's duration. After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended

at baseline (week 0). At baseline, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg or a matching placebo qd for a 12-week, double-blind, placebo-controlled treatment period that consisted of visits at weeks 4, 8 and 12 and a 30-day follow-up telephone contact or visit.

2149 patients enrolled and 1329 patients were randomized as follows:

- Full analysis set: 1270 patients: Placebo: 433 patients; mirabegron 50 mg: 425 patients; mirabegron 100 mg: 412 patients
- Full Analysis Set Incontinence (FAS-I) reflecting only those subjects with incontinence at baseline: 933 patients: Placebo: 325 patients; mirabegron 50 mg: 312 patients; mirabegron 100 mg: 296 patients
- Safety Analysis Set: 1328 patients: Placebo: 453 patients; mirabegron 50 mg: 442 patients; mirabegron 100 mg: 433 patients

Study Design: The inclusion/exclusion criteria were the same across the 3 primary efficacy and safety studies, except in Study 178-CL-046, where criteria were added to accommodate precautions for use of tolterodine.

The co-primary efficacy variables included:

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

The key secondary efficacy variables included:

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

Safety variables included:

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

- Postvoid residual volume (PVR)

Table 7: Schedule of Procedures Study 178-CL-047

Study Period	Screening	Baseline	Double-blind Treatment			Follow-up	Un-scheduled
			4	8	12		
Week	-2	0	4	8	12	Week 12 +30 days	
Visit	1	2	3	4	5	6	
Procedures							
Patient information and informed consent	X						
Demographics	X						
Medical history and OAB history	X						
Physical examination	X				X		
Medication history, OAB treatment history	X						
Cough provocation test (women only)	X						
Inclusion/exclusion criteria check	X	X					
Randomization		X					
Study drug dispensing	X	X	X	X			
Study drug compliance check		X	X	X	X		
Concomitant medication	X	X	X	X	X	X	
Patient instruction on diary completion, and pulse rate and blood pressure measurement	X	X	X	X			
Reminder call for diary completion 5 days before the visit		X			X		
Diary and questionnaire review with patient		X	X	X	X		
Safety							
Hematology and biochemistry	X	X	X	X	X		X
Urinalysis †	X						
Pregnancy test (beta-HCG in serum) ‡	X	X	X	X	X		
Vital signs	X	X §	X §	X §	X §		X
Ultrasonography or bladder scan (PVR)	X				X		
12-lead ECG	X				X		X ¶
Adverse events	X	X	X	X	X	X	
Efficacy and Pharmacokinetics							
Diary to be completed during 3 days immediately prior to visit		X	X	X	X		
OAB-q		X	X	X	X		
PPBC, TS-VAS		X			X		
EQ-5D questionnaire		X	X	X	X		
WPAI:SHP questionnaire		X			X		
Data collection on nonstudy-related physician visits for the patient's bladder condition		X	X	X	X		
Blood sampling for population pharmacokinetics ††			X	X	X		

Source: Table 1, 178-CL-047 Study Report, page 43.

During each office visit, the site recorded vital sign measurements using the patient's self-measurement device and the site's standard office measuring device. Three readings were to be taken approximately 2 minutes apart with each device. The site personnel then calculated the average value for each vital sign parameter using the last 2 of the 3 readings from each measurement device as follows:

Average of self-measurement device (AVGSM) = (measurement 2 + measurement 3)/2

Average of standard office measurement device (AVGSO) = (measurement 2 + measurement 3)/2

Then, the average of the average for each measurement device for each vital sign parameter was calculated as follows:

Average (AVG) = (AVGSM + AVGSO)/2

At baseline, the patient's blood pressure status was used to categorize the patient as either normotensive or hypertensive. A patient was categorized as normotensive at baseline if the average SBP was < 140 mm Hg and the average DBP was < 90 mm Hg at baseline; a patient was categorized as hypertensive at baseline based on the investigator's assessment. For post-baseline assessments, the investigator then used the following criteria, as defined in the protocol, to determine if a patient was considered hypertensive. Assessments were based on blood pressure measurements obtained at the office visits.

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 [World Health Organization, International Society of Hypertension, 2003].
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 to 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 of blood pressure.

Tachycardia was defined as a resting heart frequency > 100 beats per minute (bpm) measured as pulse rate.

Statistical Methods: Since there were 2 primary efficacy variables and 3 key secondary efficacy variables, the multiplicity between the variables was controlled at a type I error rate at the $\alpha = 0.05$ level using a stepwise parallel gatekeeping procedure. At each of the 5 stages, the difference between a mirabegron dose group and placebo had to be statistically significant

before a mirabegron dose group proceeded to the next stage. The stages and efficacy variables that were evaluated were as follows:

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

Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the $\alpha=0.025$ level.

The planned analyses were modestly revised as five patients were enrolled into the study on 2 separate occasions; in each case, this occurred at 2 different study sites. Of these, 4 patients were randomized twice and therefore analyzed as 8 unique patients. All preplanned efficacy and safety analyses were conducted with these patients included as 8 unique patients. Additional sensitivity analyses, excluding the 8 patient numbers assigned to these 4 patients, were conducted for the co-primary and key secondary efficacy variables.

Efficacy Results:

Table 8 : Study 178-CL-047 Coprimary and Key Secondary Efficacy Results

Co-Primary Efficacy Results	Mirabegron		
	50 mg	100 mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr (FAS-I)			
n	312	296	
Adjusted mean difference vs placebo(SE)	-0.34(0.160) p=0.026	-0.50 (0.162) p=<0.001	
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
n	425	412	
Adjusted mean difference vs placebo(SE)	-0.61 (0.188) p=0.001	-0.70 (0.189) p=<0.001	
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
n	424	412	
Adjusted mean difference vs placebo(SE)	11.1 (3.43) p=0.001	11.0 (3.45) p=0.002	
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
n	309	293	
Adjusted mean difference vs placebo(SE)	-0.48 (0.166) p=0.003	-0.46 (0.168) p=<0.001	
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
n	422	409	
Adjusted mean difference vs placebo(SE)	-0.42 (0.182) p=0.022	-0.60 (0.183) p=0.001	

Source: Table 1, Summary of Clinical Efficacy, current submission, page 9. For placebo comparisons see the following two tables.

Table 9: Study 178-CL-047 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo	Mirabegron	
		50 mg	100 mg
	(n=433)	(n=425)	(n=412)
Baseline			
Mean (SE)	11.51 (0.157)	11.80 (0.168)	11.66 (0.167)
Final Visit			
Mean (SE)	10.51 (0.164)	10.09 (0.175)	9.91 (0.166)
Change from Baseline			
Mean (SE)	-1.00 (0.140)	-1.71 (0.145)	-1.75 (0.135)
p-Value		0.001	<0.001
Statistically Superior to Placebo at the 0.05 Level With Correction for Multiplicity		Yes	Yes

Source: Table 14, Study CL-178-047, page 97

Efficacy for mirabegron 50 mg and 100 mg versus placebo for the micturitions endpoint was observed as early as week 4; each mirabegron group demonstrated a statistically significant difference from baseline to week 4 in the reduction in the mean number of micturitions per 24 hours compared to placebo with the multiplicity adjustment. At weeks 8 and 12, mirabegron 50 mg and 100 mg continued to demonstrate statistically significant differences from baseline in the reduction in the mean number of micturitions per 24 hours compared to placebo.

Table 10: Study 178-CL-047 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Placebo	Mirabegron	
		50 mg	100 mg
	(n=325)	(n=312)	(n=296)
Baseline			
Mean (SE)	3.03 (0.171)	2.77 (0.150)	2.69 (0.142)
Final Visit			
Mean (SE)	1.81 (0.152)	1.33 (0.133)	1.14 (0.128)
Change from Baseline			
Mean (SE)	-1.22 (0.152)	-1.44 (0.126)	-1.56 (0.130)
p-Value		0.026	<0.001
Statistically Superior to Placebo at the 0.05 Level With Correction for Multiplicity		Yes	Yes

Source: Table 14, Study 178-CL-047, page 96

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 mirabegron 50 mg and 100 mg groups at week 12 were similar to those at the Final Visit in the primary analysis. Both mirabegron groups demonstrated statistically significantly superior mean reduction of incontinence episodes compared to the placebo group as early as week 4 and their effectiveness was maintained throughout the treatment period (weeks 8 and 12).

The co-primary efficacy variables were summarized using the FAS-I and the FAS for the following subgroups: gender, age group (< 65, ≥ 65 and < 75, ≥ 75), race and geographical region. Interpretation of the results of subgroup analyses is limited due to disproportionate numbers of patients in the subgroups for some variables and the influence of sample size on results. There was no significant treatment group by subgroup interaction for age group, race and geographical region for the change from baseline to Final Visit in mean number of incontinence episodes per 24 hours.

The treatment by gender interaction for incontinence episodes was significant (P=0.003). Among male patients, the adjusted mean difference versus placebo was -0.77 (95% CI: 0.03, 1.50) in the mirabegron 50 mg group and 0.42 (95% CI: -0.34, 1.18) in the mirabegron 100 mg group. Among female patients, the adjusted mean difference versus placebo was -0.59 (95% CI: -0.93, -0.24) in the mirabegron 50 mg group and -0.69 (95% CI: -1.04, -0.34) in the mirabegron 100 mg group.

Reviewer's Efficacy Conclusions: The statistically significant efficacy of mirabegron (with correction for multiplicity) for the treatment of OAB has been demonstrated in this study. Mirabegron also demonstrated efficacy for the key secondary endpoints in this study. At least in the mirabegron 100 mg dose group (which is not up for approval), there appeared to be a better effect in women compared to men.

The Sponsor in their safety summary of Study 178-CL-047 states:

- The overall incidence of TEAEs was similar across the treatment groups (50.1%, 51.6% and 46.9%; placebo, mirabegron 50 mg and mirabegron 100 mg, respectively).

Table 11: Overview of Treatment Emergent Adverse Events Study 178-CL-047

Parameter, n (%)	Placebo	Mirabegron	
	(n=453)	50 mg (n=442)	100 mg (n=433)
Adverse Events	227 (50.1)	228 (51.6)	203 (46.9)
Deaths	1 (0.2)	0	1 (0.2)
Serious Adverse Events	9 (2.0)	11 (2.5)	14 (3.2)
Adverse Events Leading to Study Discontinuation	17 (3.8)	18 (4.1)	18 (4.2)

Source: Table 28, 178-CL-047 Study Report, page 119

- Two deaths were reported, 1 in the placebo group and 1 in the mirabegron 100 mg group; both deaths occurred > 30 days after the last dose of study drug.
- The overall incidence of treatment-emergent SAEs was 2.0%, 2.5% and 3.2% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.
- The overall incidence of patients who discontinued study drug due to a TEAE was 3.8%, 4.1% and 4.2% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.
- For events of interest the Sponsor summarizes:
 - The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was similar across treatment groups; there was no overt signal for mirabegron treatment.

Table 12: Hypertension AE Incidence Study 178-CL-047

Preferred Term n (%)	Placebo	Mirabegron	
	(n=453)	50 mg (n=442)	100 mg (n=433)
Hypertension	30 (6.6)	27 (6.1)	27 (6.2)

Source: Table 36, 178-CL-047 Study Report, page 133.

- No TEAEs of QTc prolongation were observed. No proarrhythmic events of ventricular tachycardia, ventricular fibrillation or torsade de pointes were reported.
- The overall incidence of arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 0.9% in the placebo group and 2.2% in the combined mirabegron groups. Overall, there were more tachyarrhythmia TEAEs in mirabegron-treated patients than in placebo-treated patients. Cases of atrial fibrillation were not observed in the placebo group but were noted in 2 (0.5%) patients treated with mirabegron 50 mg and 4 (0.9%) patients treated with mirabegron 100 mg.

Reviewer's Comment: No tachyarrhythmia was reported in placebo subjects according to Table 12.6.1.15. In the mirabegron 50 mg arm there was one report of supraventricular extrasystole, and in the mirabegron 100 mg arm there was one report each of supraventricular tachycardia and sinus tachycardia. Atrial fibrillation was noted in one subject in 50 mg mirabegron arm and two subjects in the 100 mg mirabegron arm. Tachycardia was noted in 4 (0.4%) of placebo subjects, 6 (1.4%) of mirabegron 50 mg subjects, and 3 (0.7%) of mirabegron 100 mg subjects.

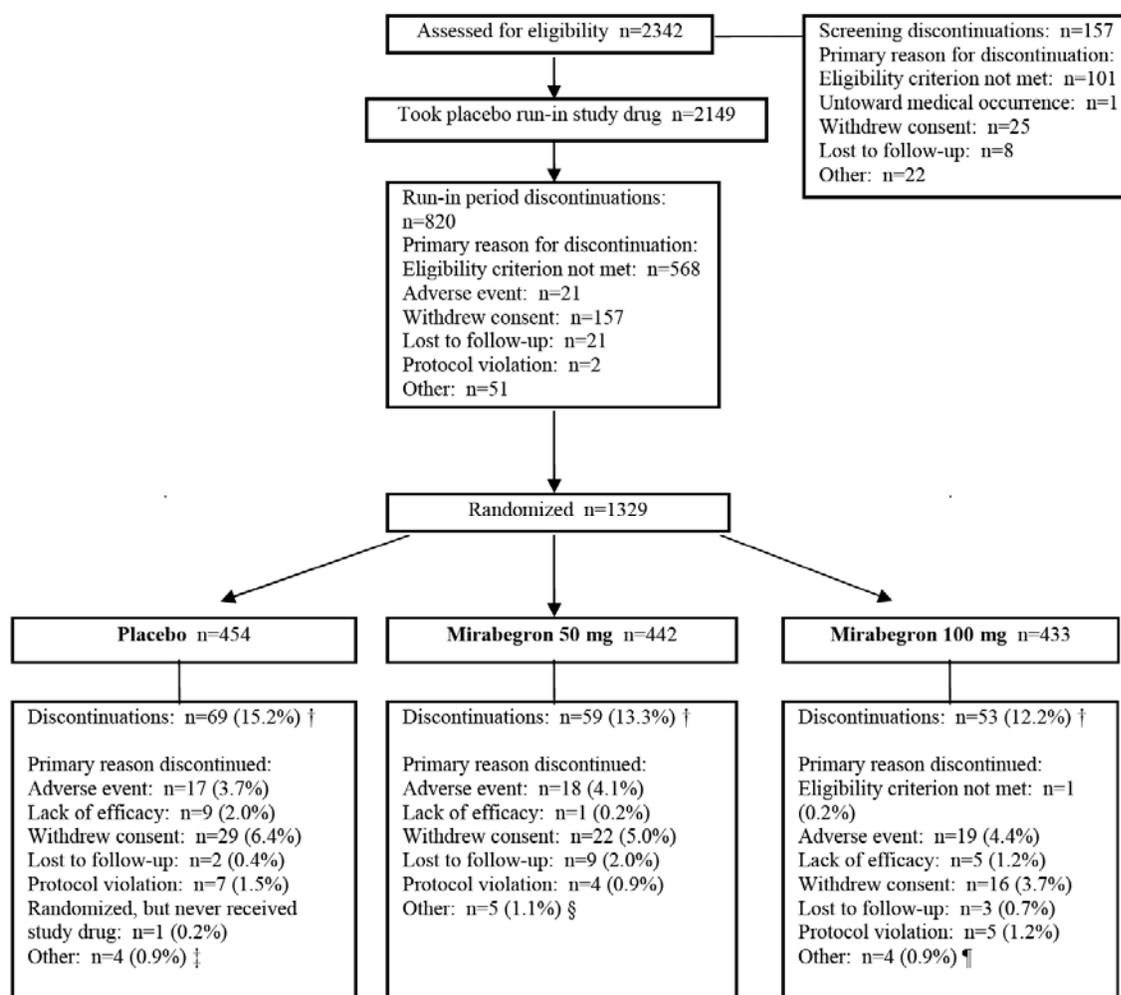
- The overall incidence of adjudicated Antiplatelet Trialists' Collaboration/Major Adverse Cardiovascular Events (APT/C/MACE) cardiovascular events was 0.9% in placebo-treated patients; there were no adjudicated APT/C/MACE events in mirabegron-treated patients. The overall incidence of adjudicated non APT/C/MACE cardiovascular events was 0.4%, 0.5% and 0.9% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.
- Acute urinary retention was not observed in mirabegron-treated patients.
- The overall incidence of events indicative of potential hypersensitivity was similar across treatment groups. One event of urticaria concomitant with hepatic dysfunction and 1 event of vasculitis were reported in patients treated with mirabegron; similar events were not reported in patients treated with placebo.
- No episodes of syncope or seizure were observed in the study.
- There was a small increase in hepatic TEAEs in drug groups compared to placebo, based on the Possible Drug-related Hepatic Disorders -Comprehensive Search SMQ. The overall incidence of hepatic TEAEs was 1.1%, 1.4% and 1.8% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. Most hepatic TEAEs were mild or moderate in intensity.
- No patients met laboratory criteria for Hy's law. The incidence of patients with hepatic parameters meeting potentially clinically significant (PCS) criteria was 0.2%, 1.1% and 1.4% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively (excluding patients with GGT values that met the PCS criterion for GGT only).
- The incidence of hepatic events when TEAEs and PCS criteria were assessed together was 2.3% in mirabegron-treated patients, regardless of treatment group, and 1.1% in placebo-treated patients.

Reviewer's Comment: There may be a modest increase over placebo of hepatic enzyme elevation events in this study. This is more appropriately evaluated in the integrated summary of safety. Hepatic SAEs and hepatic AEs resulting in discontinuation will be evaluated in this individual study review.

- Changes in hematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups.
- A dose-dependent adjusted mean difference from placebo in mean AM and PM pulse rate was observed with mirabegron treatment (AM: 1.4 and 2.3 bpm, mirabegron 50 mg and 100 mg, respectively; PM: 1.3 and 2.6 bpm, mirabegron 50 mg and 100 mg, respectively).

- Adjusted mean changes from baseline in systolic and diastolic blood pressure measurements were similar across all treatment groups and between blood pressure subpopulations (normotensive and hypertensive).
- Increases in heart rate noted on ECGs were consistent with increases in pulse rate. No consistent ECG trends were identified.
- The incidence of notable shifts in PVR was comparable across treatment groups. No mirabegron-treated patients had a PVR > 300 mL at the Final Visit. Notable shifts did not result in events that required intervention.

Figure 3: Patient Disposition Study 178-CL-047



Source: Table 2, Copy, 178-CL-047 Study Report, page 73.

Reviewer's Comment: There appear to be no discernible trends noted in patient disposition. Of the 157 patients who discontinued during screening, 101 did not meet eligibility criteria. Of the 820 subjects who discontinued during the Run-in period, 568 did not meet eligibility criteria, 21 experienced an adverse event and 157 withdrew consent. I do not feel that these discontinuations during the run-in period affects the generalizability of the study findings. Subjects lost to followup once randomized were 0.4 % for placebo, 0.8 % for mirabegron 50 mg and 0.7 % for mirabegron 100mg. It is doubtful this small incidence of lost to follow-up subjects affects trial outcome

Table 13: Common (>=2% of Patients in Any Treatment Group) Treatment Emergent Adverse Events Study 178-CL-047

MedDRA (v9.1) Preferred Term n (%)	Placebo	Mirabegron	
	(n=453)	50 mg (n=442)	100 mg (n=433)
Hypertension	30 (6.6)	27 (6.1%)	21 (4.9%)
Urinary Tract Infection	8 (1.8)	12 (2.7)	16 (3.7)
Headache	9 (2.0)	14 (3.2)	13 (3.0)
Nasopharyngitis	13 (2.9)	15 (3.4)	11 (2.5)
Upper Respiratory Tract Infection	12 (2.6)	12 (2.7)	9 (2.1)
Diarrhea	6 (1.3)	10 (2.3)	10 (2.3)
Sinusitis	10 (2.2)	9 (2.0)	9 (2.1)
Dry Mouth	7 (1.5)	2 (0.5)	9 (2.1)

Source: Table 29, Study Report 178-CL-047, page 121.

Reviewer's Comment: In this study, there was a modest increase in the incidence of urinary tract infections, headache, diarrhea, and nasopharyngitis in the mirabegron 50 mg group compared to placebo.

The incidence of hypertension as an AE was lower for mirabegron groups compared to placebo. A JMP search was performed using the AEDECOD term hypertension. Thirty-one subjects were identified. Of these subjects, 12 were identified with the AE of hypertension in the mirabegron 50 mg group. 19 were identified with terms indicating pre-existing hypertension such as exacerbation of hypertension, increase in hypertension, worsening hypertension and increase in high blood pressure. The CRFs for the 12 patients with the AE of hypertension patients were accessed. Blood pressures prior to Day 1 were evaluated. The first day that the blood pressures were measured was not considered. If the patient had multiple blood pressures (on different days) exceeding 140 mmHg systolic or 90 mmHg diastolic and was not the first of three sequential blood pressure determinations, they were considered as having pre-existing hypertension for the purposes of this analysis. This differs from the Sponsor's criteria. 8 of the 12 patients were identified as having pre-existing hypertension. 4 patients were identified as having treatment emergent hypertension. This analysis was repeated for the placebo or

mirabegron 100 groups. In the placebo arm of Study 178-CL-047, 36 patients were identified using the AEDECOD of hypertension. Of these patients, 16 patients were identified using the AETERM hypertension. 20 patients were identified with terms indicating increases in the blood pressure in the setting of pre-existing hypertension. In the mirabegron 100 arm of Study 178-CL-047, 22 patients were identified using the AEDECOD of hypertension. 12 of these subjects had AETERMs indicative of hypertension not qualified as pre-existing and 10 had AETERMs indicating pre-existing hypertension. By my analysis, new onset hypertension occurred in very few mirabegron 50 mg patients and was probably not above the population background level.

There was one death in a patient receiving mirabegron. The narrative is below:

Subject U00016176141: The patient is a 66 year old US white female randomized to 100 mg mirabegron 12 May 2008. The patient received a total of 49 days of study drug which was discontinued on Day 49 due to the adverse events of bladder cancer and metastatic colon cancer. The last visit occurred on Day 50 and the patient did not participate in subsequent mirabegron studies.

The medical history included tonsillectomy (1947), aortic insufficiency (since 1994), hypertension (since 1994), arthritis (since 1995), degenerative disc (since 1995), angioplasty (2001), polypectomy vocal cords (2001), anemia (since 2002), chronic obstructive pulmonary disease (COPD) (since 2003), colon cancer (2006), colon resection (2006), gastric ulcer (2006), hydronephrosis (2006), renal calculi (since 2007-08-21), thoracic aneurysm (since 2007-08-24), and overactive bladder (since 2007). The subject had undergone a colonoscopy on day -57 (b) (6). Anastomosis with superficial ulceration was noted in the transverse colon. No cancer was seen but a biopsy was taken. The pathology report on the biopsy specimen revealed no evidence of atypia or malignancy. Carcinoembryonic antigen (CEA) elevated at 6.2 (units and normal range not specified) was noted on day 41 (b) (6). Concomitant medications include atenolol, enalapril, isosorbide, paracetamol, iron, sucralfate, and amlodipine. The subject had been a current smoker (1 pack per day).

On Day 3 and Day 28, the patient reported the separate adverse events of hematuria which resolved. The urinalysis was not indicative of infection.

On day 38, serious adverse events of anemia, gross hematuria, bladder cancer, and metastatic colon cancer were reported. The subject had a relevant medical history of stage IV colon cancer and colon resection in 2006. The subject reportedly had undergone serial colonoscopies and upper endoscopies, the latter most recently in an outpatient setting approximately two weeks ago (medical records). On day 37 (b) (6), the subject presented to the emergency room (ER) with complaints of gross hematuria and weakness. Hemoglobin values on days -14, 1, and 29 were 83, 81, and 89 g/L (reference range 116 - 154 g/L), respectively and hematocrit fraction values were 0.25, 0.24, and 0.27 (reference range 0.34 - 0.45 fraction), respectively. Upon arrival at the ER, the subject was noted to have a hematocrit of 17.1 and hemoglobin of 5.9 and urinalysis showed a large amount of blood (units and reference range not provided) (hospital

discharge summary). The subject was admitted to the hospital and was given a transfusion of two units packed red blood cells. On day 38, the subject had a cystoscopy with bladder biopsy, bilateral retrograde ureteropyelogram, bilateral double J stent and transurethral resection of a bladder tumor (TURBT). A mass was found in the bladder and the frozen section was consistent with metastatic colonic adenocarcinoma (biopsy report (b) (6)). Further biopsies were taken. The bladder tumor was flat, elongated and 7 cm in greatest diameter. Pathology came back as possibly indicative of an extrinsic or non-urothelial origin tumor. The subject was put on chronic bladder irrigation (CBI). The subject developed constipation and postoperatively she was seen in consultation by gastrointestinal (GI) service and medical management was instituted to help relieve constipation. The subject's hematuria gradually receded, CBI was discontinued and the subject was discharged for follow up with urology (hospital discharge summary).

On day 47, the subject was readmitted to the hospital for hematuria. Upon readmission, the subject reported having some constipation, slight abdominal pain and was using oxycodone/paracetamol as needed for pain. She did not have any rectal bleeding and denied nausea and vomiting (hospital medical records). On day 47, laboratory values were: white blood count 7.5, hemoglobin 7.2, hematocrit 25%, and platelets were 268 (reference ranges not provided). The subject did have hematuria and was started on CBI. On day 49, the subject had a cystoscopy with evacuation of clots and fulguration of bleeders. The subject had clots removed and fulguration to control bleeding and to avoid further complications prior to starting chemotherapy.

On day 99 (b) (6) the subject expired due to stage IV colon cancer with metastases to the bladder. No autopsy report was available.

Reviewer's Comment: Hematuria dates to Day 3, suggesting that the bladder lesion (metastatic colon cancer) and that recurrent colon cancer was present at baseline. In my opinion, neither this cancer nor death are attributable to mirabegron.

Table 14: Serious Treatment-Emergent Adverse Events Study 178-CL-047

MedDRA (v9.1) System Organ Class Preferred Term n (%) 178-CL-047	Placebo (n=453)	Mirabegron	
		50 mg (n=442)	100 mg (n=433)
Any Serious Adverse Event	9 (2.0)	11 (2.5)	14 (3.2)
Cardiac Disorders	2 (0.4)	2 (0.5)	3 (0.7)
Atrial Fibrillation	0	1 (0.2)	1 (0.2)
Angina Pectoris	0	1 (0.2)	0
Cardiac Failure	0	0	1 (0.2)
Supraventricular Tachycardia	0	0	1 (0.2)
Acute Coronary Syndrome	1 (0.2)	0	0
Coronary Artery Disease	1 (0.2)	0	0
Infections and Infestations	3 (0.7)	3 (0.7)	2 (0.5)
Appendicitis	0	0	1 (0.2)

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Clostridial Infection	0	1 (0.2)	0
Gastroenteritis	0	1 (0.2)	0
Pneumonia	1 (0.2)	1 (0.2)	0
Sepsis	0	0	1 (0.2)
Cellulitis	1 (0.2)	0	0
Localized Infection	1 (0.2)	0	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	1 (0.2)	3 (0.7)	2 (0.5)
Prostate Cancer	0	2 (0.5)	0
Bladder Cancer	0	0	1 (0.2)
Colon Cancer Metastatic	0	0	1 (0.2)
Lung Carcinoma Cell Type Unspecified Recurrent	0	0	1 (0.2)
Malignant Melanoma	0	1 (0.2)	0
Metastases to Lymph Nodes	0	1 (0.2)	0
Lung Neoplasm Malignant	1 (0.2)	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	3 (0.7)	1 (0.2)
Cervical Spinal Stenosis	0	1 (0.2)	0
Lumbar Spinal Stenosis	0	0	1 (0.2)
Osteoarthritis	0	1 (0.2)	0
Spinal Column Stenosis	0	1 (0.2)	0
Tenosynovitis	1 (0.2)	0	0
General Disorders and Administrative Site Conditions	0	0	3 (0.7)
Chest Pain	0	0	3 (0.7)
Renal and Urinary Disorders	1 (0.2)	1 (0.2)	2 (0.5)
Calculus Ureteric	0	0	1 (0.2)
Hematuria	0	0	1 (0.2)
Renal Failure Acute	0	1 (0.2)	0
Urinary Retention	1 (0.2)	0	0
Injury, Poisoning and Procedural Complications	0	0	2 (0.5)
Cerebral Hemorrhage Traumatic	0	0	1 (0.2)
Post Procedural Hematoma	0	0	1 (0.2)
Surgical and Medical Procedures	1 (0.2)	2 (0.5)	0
Angioplasty	0	1 (0.2)	0
Gastric Banding	0	1 (0.2)	0
Shoulder Arthroplasty	1 (0.2)	0	0
Blood and Lymphatic System Disorders	0	0	1 (0.2)

Anemia	0	0	1 (0.2)
Gastrointestinal Disorders	1 (0.2)	0	0
Vomiting	1 (0.2)	0	0
Nervous System Disorders	1 (0.2)	0	0
Ischemic Stroke	1 (0.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	0	0
Pulmonary Embolism	1 (0.2)	0	0
Vascular Disorders	1 (0.2)	0	0
Pulmonary Embolism	1 (0.2)	0	0

The AEs are tabulated by SOC. Preferred terms within SOC are listed based on reviewer's opinion of relevance and if a disproportion on incidence is present.

Source: Table 32, Study Report 178-CL-047, page 123.

Reviewer's Comment: No single SAE was reported by more than 1 subject in this study.

SAE Selected Narratives in Brief:

Subject U00016297440: Prostate Cancer: The subject is a 64 year old white US male randomized to mirabegron 50 mg (b) (6). He received 28 days of study drug and discontinued due to the adverse event of prostate cancer on Day 28. On Day 7, the patient's primary care physician noted an abnormal prostate exam as part of a routine prostate exam. Prostate biopsy revealed adenocarcinoma Gleason's score of 7 (grades 3 and 4) in 2 of 2 cores (11% of submitted tissue) obtained from the left mid prostate. 7% of the cores from the right base had Gleason's score 6 (3 + 3). A skeletal bone scan was negative for metastases. The subject underwent radiation treatment followed by radioactive seed implantation on Day 138. CT scan of the abdomen and pelvis on Day 761 secondary to a diagnosis of prostatitis showed no evidence of mass lesion in the pelvis.

Date	Study Day Relative to Start of Study 178-CL-047	PSA Value (ng/mL) (normal range 0 – 4.0 ng/mL)
(b) (6)	7	3.37
(b) (6)	20	3.39
(b) (6)	187	0.70
(b) (6)	347	0.20

Date	Study Day Relative to Start of Study 178-CL-047	PSA Value (ng/mL) (normal range 0 – 4.0 ng/mL)
(b) (6)	489	0.1
(b) (6)	580	<0.1

Source: Copy Table 2 from Patient Narrative

Reviewer's Comment: Because of the time course, a causal association between this cancer and mirabegron is highly unlikely.

Subject U00016176141: Metastatic Colon Cancer: Death: See Death Narrative. It is to be noted that this patient was reported to have had bladder cancer but upon review of the case narrative, this patient had metastases of known colon cancer to the bladder.

Subject U00019436876: Prostate Cancer: The subject is a 49 year old white US male randomized to mirabegron (b) (6). The subject received 90 days of study drug which was not discontinued due to the adverse event. On day 90, during the study physical examination the physician noted an induration at the right laterobasilar aspect of the prostate. The prostate specific antigen (PSA) was 2.3 ng/mL (no reference range provided). An adverse event of induration right laterobasilar aspect of prostate was reported on day 90. The investigator considered this adverse event to be moderate and not related to study drug. On day 109, the subject had a prostate biopsy that was positive for adenocarcinoma. On day 202 (b) (6), the subject was admitted to the hospital and underwent a radical prostatectomy. The final pathology report revealed Gleason 3+4=7 adenocarcinoma confined to the prostate.

It is notable that asymmetric enlargement of the right lobe of the prostate was noted on Day -15 by the investigator. On Day 90, induration was noted “suggesting tumor growth” by the investigator. A bone scan and CT scan on Day 127 showed no evidence of metastatic lesions. The event was treated by a radical prostatectomy. It is also notable that the subject had PSA value of 10.50 ng/mL on Day -309 (9 July 2007).

Reviewer’s Comment: It seems apparent that this subject’s prostate cancer pre-dated the initiation of study medication. The Committee assessed that there was evidence of a relevant pre-existing condition. The Investigator noted an asymmetric enlargement of the right lobe of the prostate without induration on day -15. This was the pre-existing condition that might have been a tumor. Induration was newly noted on day 90 suggesting tumor growth. Given the natural history of prostate cancer, it was almost certainly present at baseline. Mirabegron was not causally associated with the adverse event of prostate cancer, but the Committee stated “In 90 days, it seems possible that a drug could produce tumor stimulation manifesting as new induration.” I cannot assign causality to mirabegron in this case.

Subject U00021787330: Lung Neoplasm Malignant: The subject is a 72 year old white US female randomized to placebo. Onset of tumor was Day 21.

Subject U00016176141: Malignant Melanoma, Metastases to Lymph Nodes: The subject is a 71 year old white US male randomized to mirabegron 50 mg 15 August 2008. He received a total of 84 days of mirabegron and completed the study. On day 20, a serious adverse event of left shoulder melanoma was reported and on day 63, a serious adverse event of sentinel lymph node melanoma (metastases to lymph nodes) was reported. The subject had a relevant medical history of actinic keratosis.

Reviewer's Comment: The Neoplasm Adjudication Committee review stated that metastatic melanoma developing within 20 days of study drug treatment was not consistent with known mechanisms of tumor formation or stimulation. I agree.

Subject U00021866960: Recurrence of Cancerous Growth Right Lung: The subject is an 85 year old white US male randomized to mirabegron 100 mg on 23 July 2008. He received 15 days of study drug. In 2002, he underwent surgical removal of a cancerous tumor from the right lung. On day 17, an MRI scan revealed a recurrence of the cancerous tumor on the right lung. While no documentation of a biopsy was obtained, it was learned subsequently that the patient had undergone chemotherapy and was to receive radiotherapy.

Reviewer's Comment: The time course of events (after 17 days of treatment) is not consistent with mirabegron being causal in this cancer recurrence.

Subject U00016176141: Bladder Cancer: This is the same patient who succumbed to metastatic colon cancer. Upon review of the case narrative, this patient had metastatic colon cancer to the bladder and not bladder cancer.

Reviewer's Comment: Study 178-CL-047 had an increased of neoplastic adverse events relative to the other 2 pivotal studies. In two instances, cases were reported twice with two different neoplastic preferred terms. In no instance, in my opinion, was the time course compatible with mirabegron as causal. There is one possible instance where the Neoplasm Adjudication Committee suggested possible tumor growth stimulation. I do not agree with that suggestion. New malignant events in short-term studies in the total mirabegron group equal eight and seven of those events come from Study 178-CL-047 (page 51 of Neoplasm Research Report).

Subject U00001667869: Gastroenteritis/ Renal Failure: The subject is a 75 year old white Canadian female randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The study drug was discontinued on Day 59 due to the adverse events acute renal failure and acute gastroenteritis. Past significant history includes swollen legs (since 2007) and hypertension (since August 2008). Concomitant medications include alendronic acid, bisoprolol, and spironolactone.

On day 50, a serious adverse event of acute gastroenteritis was reported. Subject had a relevant medical history of cholecystectomy, dilation of esophagus, esophageal spasm and mild fecal incontinence. The subject had an episode of incontinence of stool while in a store. She went home and had a few bowel movements that night and continued having multiple watery bowel movements every one to two hours. On day 56, she had defecated 5 times prior to going to the emergency room. On day 57, the subject was diagnosed with dehydration and was admitted to the hospital for intravenous fluids and work-up. Laboratory results were serum creatinine level to 197 (units and reference range not reported) as well as elevated white blood cell count to 13,000 (units and reference range not reported). Fecal occult blood was negative. On day 57, an abdominal ultrasound revealed previous cholecystectomy. Common bile duct was dilated 10.2 mm with mild dilatation of the proximal intrahepatic ducts. Stool cultures were negative and Clostridium difficile toxin on two occasions was negative. On day 59, a sigmoidoscopy revealed

a normal exam to the cecum. There was diffuse mucosal edema, but no ulcerations nor pseudomembranes, but changes consistent with probable infectious colitis. Pathology demonstrated only non-specific chronic inflammation. During hospitalization, stools continued to be watery, profuse and very foul smelling. On day 56, a serious adverse event of acute renal failure was reported. This serious adverse event occurred during the subject's hospitalization and was associated with the events of the acute gastroenteritis.

Study Day	Blood Creatinine	White Blood Count	Haemoglobin	Blood Urea	Sodium
day 57	197	13.0	156	no results available	128
day 59	54	9.9	121	4.3	135
day 66	normal	normal	110	normal	no results available

* reference ranges not available

Source: Copy Table 2 of patient narrative. Days 57 and 59 reflect hospital lab values (while units are not stated the upper limit of normal for blood creatinine is <133 µmol/L). The BUN on Day 29 was 3.9 (nl range 3.6-7.1 mmol/L) and the creatinine was 50.

On day 66, the subject was discharged from the hospital with a diagnosis of acute gastroenteritis, likely viral and acute renal failure. From day 66 to day 76, the subject was given cholestyramine orally for a total daily dose of 8 grams and loperamide orally for a total daily dose of 2mg times 10 days plus 2 mg after each loose bowel movement for the indication of gastroenteritis. At the time of discharge, the subject was able to control her bowels for up to a few hours at a time. On day 72, the serious adverse event of acute renal failure was reported as resolved. On day 80, the serious adverse event of acute gastroenteritis was reported as resolved.

Reviewer's Comment: The most likely diagnosis to explain the above events is viral gastroenteritis and pre-renal azotemia secondary to dehydration. I cannot attribute these AEs to the study drug.

Subject 1529-8351: Angina Pectoris/ Angioplasty: The subject is a 75 year old white US female randomized to mirabegron 50 mg on (b) (6). The subject received a total of 94 days of study drug. The study treatment was not discontinued due to the adverse event. The medical history included myocardial infarction (since unknown), history of seizures (1943 through 2008- 11-01), chronic fatigue syndrome (since 1950), fibromyalgia (since 1960), hypothyroidism (since 1963), hysterectomy (1966), basal cell carcinoma (1998 through 2008), night blindness (since 1998), cerebrovascular accident (CVA) (1999), hypertension (since 1999), bladder lift (2000), chronic venous stasis (since 2000), right endarterectomy (2000), coronary artery disease (CAD) (since 2002), gastroesophageal reflux disease (GERD) (since 2002-12), bilateral renal stents (2004-07-14), kidney stents (2004-07-14), allergy to bentyl causing anaphylactic reaction (since 2005), allergy to Cardizem, codeine, Demerol, sulfa (since 2005), angioplasty (2005), hypercholesterolemia (since 2005), carotid artery endarterectomy (2005-07), transient ischemic attack (TIA) (2005-09), depression (since 2008), esophageal dilation (2008 through 2008-07), esophageal stricture (2008 through 2008-07), stent placement coronary (2008-02-13), cholecystitis (since 2008-04-04), cerumen impaction (2008-05 through 2008-08-15), temporomandibular joint disease (TMJ) (since 2008-05), abnormal auditory perception (since 2008-07-15), angina (since 2008-08), deviated nasal septum (since 2008-08-15), bladder

cystocele (since 2008-09-25), prolapsed vaginal walls (since 2008-09-26). On going medications include nifedipine, atenolol, olmesartan, lansoprazole, lovastatin, natural thyroid, furosemide, and potassium.

On day 31, a serious adverse event of worsening angina was reported. The subject had a relevant medical history of hypertension, CVA, myocardial infarction, right endarterectomy, CAD, hypercholesterolemia, angioplasty, carotid artery endarterectomy, TIA, angina, and coronary stents x 2 placement. The subject's ECG at screening (day -15) was normal. The subject presented on day 31 with worsening intermittent angina for the past few weeks. The subject reported that the chest pain was more squeezing in nature than before. The subject had shortness of breath and felt dizzy, but did not lose consciousness. On day 33, an ECG revealed sinus rhythm with no acute changes. On day 34, a serious adverse event of angioplasty was reported. As a result of the serious adverse event of worsening angina, the subject underwent a cardiac catheterization followed by an angioplasty. No changes were made to study drug due to this event. No changes were made to study drug due to this event. On day 66, the subject was started on glyceryl trinitrate orally for a total daily dose of 4 mg for the indication of angina. The serious adverse event of worsening angina was reported as not resolved at the time of study completion.

Reviewer's Comment: As the Sponsor states in the patient narrative, this subject had significant coronary vascular disease for nine years prior to study entry. She has suffered a previous MI, had intermittent angina, and had previous coronary angioplasty. The subject continued to experience numerous cardiac events despite aggressive medical management, endarterectomies, and stent placements and had been experiencing increased frequency of episodes of angina. The angina had begun several months after the last procedure and a few months prior to study entry. It had worsened to the point that another cardiac catheterization and angioplasty were required. I do not feel there was sufficient evidence to implicate mirabegron with respect to this SAE.

Subject 2179-7843: Atrial Fibrillation/ Cervical Spinal Stenosis: The subject is a 66 year old white US male randomized to mirabegron 50 mg on (b) (6). The subject received a total of 28 days of study drug. The study treatment was discontinued due to the adverse event of rapid atrial fibrillation on day 28 (b) (6). The medical history included hypercholesterolemia (since 1988), gastroesophageal reflux disease (GERD) (since 2000), hearing loss (since 2000), hypertension (since 2002), enlarged prostate (since 2005), cervical spine osteoarthritis (since 2006), electrical stimulation (2007-03 through 2008-03), pinched nerve elbow area (since 2007-07) and constipation (since 2008). Ongoing medications include omeprazole, atorvastatin and lisinopril.

On Day 15, a serious adverse event of worsening of cervical spinal stenosis was reported. Patient underwent a cervical laminectomy. The subject had a relevant medical history of cervical spine osteoarthritis and electrical stimulation. There were no concomitant medications noted and there were no changes to study drug treatment due to this serious adverse event.

On Day 27, an adverse event of tachycardia was reported. There were no concomitant medications noted and no changes made to study drug due to this adverse event. The site's

review of the subject's diary showed that the heart rate elevation began on day 27, with the highest recorded heart rate of 132 bpm. An ECG was not performed. The site considered the heart rate as normal on day 28, with the highest recorded heart rate of 80 bpm. On day 28, the adverse event of tachycardia was reported as resolved.

On day 27, an adverse event of tachycardia was reported. There were no concomitant medications noted and no changes made to study drug due to this adverse event. The site's review of the subject's diary showed that the heart rate elevation began on day 27, with the highest recorded heart rate of 132 bpm. An ECG was not performed. The site considered the heart rate as normal on day 28, with the highest recorded heart rate of 80 bpm. On day 28, the adverse event of tachycardia was reported as resolved. On day 29, the subject was taken to the urgent care center and was subsequently transferred to a local hospital for evaluation. The subject was hospitalized for one day. The subject reportedly consulted with a cardiologist and reported no further problems. It was noted that the subject would not sign for medical release and therefore no further information was available. On day 29, study drug was discontinued due to this serious adverse event of rapid atrial fibrillation. On day 30, this serious adverse event of rapid atrial fibrillation was reported as resolved.

Reviewer's Comment: A causal association of the event of cervical spinal stenosis worsening is unlikely. The event of atrial fibrillation is temporally related to mirabegron, there are no other factors that appear causative, and a causal association between mirabegron and the event cannot be excluded..

Table 15: Treatment Emergent Adverse Events Leading to Discontinuation Study 178-CL-047

MedDRA (v9.1) System Organ Class Preferred Term n (%) 178-CL-047	Placebo (n=453)	Mirabegron	
		50 mg (n=442)	100 mg (n=433)
Any Adverse Event	17 (3.8)	18 (4.1)	18 (4.2)
Gastrointestinal Disorders	4 (0.9)	4 (0.9)	1 (0.2)
General Disorders and Administrative Site Conditions	0	4 (0.9)	1 (0.2)
Vascular Disorders	1 (0.2)	3 (0.7)	2 (0.5)
Hypertension	1 (0.2)	2 (0.5)	2 (0.5)
Vasculitis	0	1 (0.2)	0
Investigations	2 (0.4)	2 (0.5)	2 (0.5)
Blood Pressure Increased	1 (0.2)	0	2 (0.2)
Alkaline Phosphatase Increased	0	1 (0.2)	0
Bilirubin Increased	0	1 (0.2)	0
Blood Pressure Diastolic Increased	0	1 (0.2)	0
Platelet Count Decreased	0	0	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	2 (0.4)	2 (0.5)	2 (0.5)
Cardiac Disorders	0	1 (0.2)	2 (0.5)
Atrial Fibrillation	0	1 (0.2)	0
Palpitations	0	0	1 (0.2)
Supraventricular Tachycardia	0	0	1 (0.2)
Nervous System Disorders	1 (0.2)	1 (0.2)	2 (0.5)
Dizziness	0	1 (0.2)	0
Headache	1 (0.2)	0	1 (0.2)
Sciatica	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	1 (0.2)	0	3 (0.7)
Erythema	0	0	1 (0.2)
Pruritis	0	0	1 (0.2)
Purpura	0	0	1 (0.2)
Rash	0	0	1 (0.2)
Rash Generalized	0	0	1 (0.2)
Urticaria	1 (0.2)	0	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	1 (0.2)	1 (0.2)	1 (0.2)
Bladder Cancer	0	0	1 (0.2)

Colon Cancer Metastatic	0	0	1 (0.2)
Prostate Cancer	0	1 (0.2)	0
Lung Neoplasm Malignant	1 (0.2)	0	0
Renal and Urinary Disorders	2 (0.2)	1 (0.2)	1 (0.2)
Renal Failure Acute	0	1 (0.2)	0
Renal Impairment	0	0	1 (0.2)
Urinary	1 (0.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders	3 (0.7)	2 (0.5)	0
Asthma	0	1 (0.2)	0
Chronic Obstructive Pulmonary Disease	0	1 (0.2)	0
Dyspnea	2 (0.42)	0	0
Nasal Dryness	1 (0.2)	0	0
Injury, Poisoning and Procedural Complications	0	0	1 (0.2)
Cerebral Hemorrhage Traumatic	0	0	1 (0.2)
Psychiatric Disorders	0	0	1 (0.2)
Depression	0	0	1 (0.2)
Eye Disorders	2 (0.4)	0	0
Metabolism and Nutrition Disorders	1 (0.2)	0	0
Reproductive System and Breast Disorders	1 (0.2)	0	0

The AEs are tabulated by SOC. Preferred terms within SOC are listed based on reviewer's opinion of relevance and if a disproportion on incidence is present.

Source: Table 34, Study Report 178-CL-047, page 126.

Reviewer's Comment: The only AE leading to discontinuation reported by more than 1 patient was hypertension (n=2 in both mirabegron 50 mg and 100 mg groups).

Selected Narratives in Brief:

Subject U00016256505: Increase in Diastolic Blood Pressure: The subject is a 60 year old white US female randomized to mirabegron 50 mg on 17 June 2008. The medical history is significant for no reported past history of hypertension. The subject received a total of 32 days of study drug which was discontinued due to the adverse event of increase in diastolic blood pressure on Day 32. Concomitant medications include acyclovir, levothyroxine, zolpidem, acetylsalicylic acid, psyllium, and esomeprazole.

On day -15, an adverse event of left anterior hemiblock was reported. The subject had a baseline ECG prior to the administration of study drug that the investigator determined to be abnormal for left anterior hemiblock. The adverse event was reported as not resolved at the time of study completion. On day 39, the ECG was determined by the investigator to be normal (no left

anterior hemiblock reported). The investigator determined the event of left anterior hemiblock to be mild and not related to study drug.

On day 28, an adverse event of increase in diastolic blood pressure was reported. On day 32, study drug was discontinued due to this adverse event of increase in diastolic blood pressure. No concomitant medications were noted for this adverse event. Individual blood pressure readings demonstrated incidents of elevated diastolic BP measurements prior to the administration of study drug. On day -15, the diastolic BP was 101 mmHg and 102 mmHg, on day -5, the diastolic BP was 90 mmHg, on day -4, the diastolic BP was 86 mmHg and 88 mmHg, on day -3, the diastolic BP was 91 mmHg, on day -2, the diastolic BP was 88 mmHg, and on day -1, the diastolic BP was 88 mmHg. On day 28, the highest recorded diastolic BP was 97 mmHg and the diastolic BP remained elevated until day 39 when the highest recorded diastolic BP was 90 mmHg. On day 39, the adverse event of increase in diastolic blood pressure was reported as resolved. The investigator determined this adverse event of increase in blood pressure to be moderate and possibly related to study drug. The average blood pressures at Baseline were: Home Device 110/81 mm Hg and Office Device 114/76 mm Hg respectively. The average blood pressures at week 4 were: Home Device 116/92 mm Hg and Office Device 115/93 mm Hg respectively.

Reviewer's Comment: Severe episodes of elevations of the diastolic blood pressure were documented at screening (diastolic BP > 100 mm Hg), but between Days 28 and 39 they appeared to be more persistently elevated in the opinion of the investigator. While a causal association with mirabegron cannot be ruled out, such a conclusion is confounded by the significantly elevated blood pressures prior to baseline.

Subject U00022257773: Worsening Hypertension: The subject is a 73 year-old US female randomized to mirabegron 50 mg on 2 October 2008. The study treatment was discontinued on Day 63 due to the adverse event of worsening hypertension on day 63 (2008-12-03). The patient has a history of hypertension since 1985. She was maintained on Diovan for blood pressure control. On day 29, the adverse event of worsening hypertension was reported. Prior to screening the subject was taking Diovan (valsartan) 40 mg daily. Her baseline blood pressures in mmHg were 124/91 (home device) and 118/85 (office device). The respective blood pressures at Week 4 were 165/113 and 162/106 mmHg. At Week 8, the respective blood pressures were 169/116 and 161/102 mmHg.

Reviewer's Comment: The role of mirabegron in this worsening of cannot be causally excluded.

Subject U00021857652: Worsening Hypertension: The subject is an 85 year old US male randomized to mirabegron 50 mg on 24 September 2008. The study treatment was discontinued due to the adverse event of worsening hypertension on day 63 (25 November 2008). The subject had a past history of hypertension treated with ramipril since 2005. The subject's blood pressure during the screening period were noted as a high of 155/103 mmHg on day -4 and 160/102 mmHg on day -3. At baseline the blood pressures in mmHg were 122/71 (home device) and 120/72 (office device). At Week 4, the respective blood pressures for home device and office

device were 143/84 and 144/88 mmHg. At Week 8, the respective blood pressures for home and office devices were 166/91 and 166/91 mmHg.

Reviewer's Comment: In looking at the patient CRF, by my analysis, this patient had wide swings of the blood pressure prior to baseline and the post-baseline blood pressures seem to show a similar pattern but perhaps slightly higher. With dechallenge on Day 76 the blood pressure ranges were 129-142 mmHg systolic and 70-73 mmHg diastolic. There had been no changes in the blood pressure medications. While I cannot exclude mirabegron as playing a role in this event, it is confounding by the patient's significant hypertension at baseline.

Subject U00022528275: Liver Enzyme Elevations/ Worsening Hypertension: The subject is an 80 year old African American female randomized to mirabegron 50 mg 24 November 2008. The subject received a total of 29 days of study drug. The study treatment was discontinued due to the adverse events of increased alkaline phosphatase (ALKP), increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased total bilirubin, and increased gamma-glutamyltransferase (GGT) on day 29 (2008-12-22). The patient has a history of hypertension treated with losartan since 1990. On Day -1 and Day 22, patient reported the adverse events of nausea and vomiting which resolved each time in 1-2 days. On Day 29, the adverse event of hypertension was reported. On Day 27, an AM blood pressure was 177/116 mmHg (third of three determinations) and a PM blood pressure was 178/144 mmHg (second determination). At the time of study completion, the adverse event of worsening hypertension was reported as not resolved. At baseline the blood pressures in mmHg were 110/63 (home device) and 122/68 (office device). At Week 4 the respective blood pressures in mmHg were 164/82 (home device) and 175/82 (office device).

Reviewer's Comment: The blood pressure readings in the CRF indicate an upward trend in the blood pressure. A causal association with mirabegron cannot be ruled out.

Reviewer's Comment: Within studies 178-CL-046 and 178-CL-047, in patients taking mirabegron, there were 5 adverse event reports (two in Study 178-CL-046 and 3 in Study 178-CL-047) of worsening hypertension resulting in study discontinuation. Two of the cases noted in Study 178-CL-047 are confounded by elevated blood pressures at screening. There is also a report of worsening hypertension for the 100 mg mirabegron dose in the 047 study (U00016676826). The incidence of worsening hypertension was searched for in the AE database. The overall search term in the AETERM listing was hypertension. Modifying terms were exacerbation, aggravated, worsening, increase, or uncontrolled, and crisis. These terms were reported in 12 placebo subjects, 6 mirabegron 100 mg subjects and 11 mirabegron 50 mg subjects. In my opinion, it appears that mirabegron does not exacerbate existing hypertension in this study at a greater rate than placebo.

On day 29, adverse events of increased AST, increased ALT, increased ALKP, increased total bilirubin, increased GGT, and increased blood glucose level were reported. The subject had a relevant medical history of diabetes mellitus type II. The study drug was withdrawn.

Study Day	Alanine Amino Transferase (ALT) (normal range 1 – 30 U/L)	Aspartate Amino Transferase (AST) (normal range 1 -32 U/L)	Alkaline Phosphate (ALKP) (normal range 31 -121 U/L)	Total Bilirubin (normal range 0 – 18.6 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 – 32 U/L)	Blood Glucose (normal range 3.9– 7.8 mmol/L)
day -18	14	23	172	2.7	14	12.0
day 1	15	25	163	3.4	13	14.3
day 29	209	109	309	19.2	344	18.3
day 36	58	35	274	10.3	211	8.7
day 71	11	18	175	3.3	32	17.0

Source: Table 3, Patient U00022528275, narrative.

Reviewer’s Comment: This patient had mild elevation of hepatic enzymes which seems to have improved with mirabegron dechallenge . The patient had alkaline phosphatase above the upper limit of normal at baseline. She had also recently started rosuvastatin and sinus congestion medication. This confounds attribution to mirabegron, but with the positive dechallenge a causal association with mirabegron cannot be ruled out.

Subject U00018156541: Lymphocytic Vasculitis: The subject is a 76 year old white Canadian female randomized to mirabegron 50 mg 18 June 2008. The subject received a total of 26 days of study drug. The study treatment was discontinued due to the adverse event of lymphocytic vasculitis on Day 26 (2008-07-13). Relevant medical history includes: asthma (since 1995), seborrheic dermatitis (since 2002), allergy to imipramine (since 2004-01-31), possible transitory ischemia attack (2006), post tibial tendonitis (since 2006-05), vitamin B-12 deficiency (2007-03 through 2007-06), aphthous stomatitis (2008-02 through 2008-05), allergies to erythromycin, codeine, cephalexin, penicillin, sulfa, tetracycline and nitrofurantoin (since 2008-05-15). Concomitant medications include: budesonide with formoterol, albuterol, mometasone, eye drops for blepharitis (3), alendronic acid, cholecalciferol, ciclopirox, eflornithine (topical), terbinafine (topical), and triamcinolone oral.

On Day -3, an adverse event of aphthous stomatitis was reported. The subject was given triamcinolone orally as needed for the indication of aphthous stomatitis. On Day 45, this adverse event was reported as resolved. The investigator considered this adverse event to be moderate and not related to study drug.

On Day 21, an adverse event of lymphocytic vasculitis was reported. Physical examination findings showed a change from baseline of lymphocytic vasculitis bilateral legs (anterior). The investigator considered this change to be clinically significant. On Day 26, study drug was discontinued due to the adverse event of lymphocytic vasculitis. The subject was given

betamethasone topically at 0.1% and hydroxyzine orally for a total dose of 10mg for the indication of lymphocytic vasculitis. The diagnosis of lymphocytic vasculitis was made by punch biopsy histopathology report upon orders from the subject’s dermatologist. The histopathological description showed discrete perivascular lymphocytic infiltrate associated with rare eosinophils and extravasated erythrocytes as well as fibrinoid necrosis of the vascular endothelium. There were no neutrophils visible in the punch biopsy specimen. Relevant hematology and liver chemistries are reported in Table 2 and Table 3. Urinalysis results at screening (Day -15) were negative for RBCs; no additional urinalysis results were reported. At the time of study completion, the adverse event of lymphocytic vasculitis was reported as recovering.

Study Day	Erythrocytes (normal range 3.68 – 5.09 10 ¹² /L)	Hemoglobin (normal range 116 - 154 g/L)	Hematocrit (normal range 0.34 – 0.45 fraction)	Leukocytes (normal range 3.6 – 10.0 10 ⁹ /L)	Eosinophils (normal range 0 – 480 10 ⁶ /L)	Platelets (normal range 145 - 390 10 ⁹ /L)
day -15	4.06	138	0.40	8.9	140	289
day -1	3.84	132	0.38	8.7	70	269
day 28	4.07	138	0.41	7.3	280	239

Study Day	Alanine Amino transferase (ALT) (normal range 1 - 30 U/L)	Aspartate Amino transferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphatase (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0.0 – 18.6 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 -32 U/L)
-15	15	19	58	10.4	22
-1	16	19	50	7.4	19
28	17	19	57	8.6	20

Sources: Tables 2 and 3 of patient narrative.

Reviewer’s Comment: The subject had a medical history of dermatologic and immunologic conditions including multiple drug allergies, asthma, seborrheic dermatosis, and aphthous stomatitis. The patient was using topical bacitracin-polymixin that was started 8 day prior to the event. The Hypersensitivity Expert Committee review assessed this hypersensitivity reaction as a definite hypersensitivity reaction. The Committee noted positive dechallenge without medical treatment, did not provide an alternative explanation, and assessed leukocytoclastic vasculitis as possibly related to study drug. Lacking a clear alternative, and given a positive de-challenge, a causal association with mirabegron cannot be ruled out. Consideration should be given to include this adverse event in labeling.

Clinical Laboratory Evaluations

Hematology

Mean changes from baseline to each visit in hematology variables were similar across the treatment groups; mean changes from baseline in all analytes were of small magnitude compared

to the normal range of the analyte. No trends in the change from baseline were observed between the mirabegron and placebo groups in these parameters.

2/433 placebo patients, 3/422 mirabegron 50 mg patients and 2/418 mirabegron 100 mg patients were noted to have low platelets ($<120 \times 10^9/L$) during the study course. 50 mg mirabegron patients #1625-7709 and #2223-7476 entered the study with platelet counts of $129 \times 10^9/L$ and $125 \times 10^9/L$ respectively. The nadir values for these patients were $116 \times 10^9/L$ on Day 31 and $119 \times 10^9/L$ on Day 62. Their values at study end were $136 \times 10^9/L$ and $142 \times 10^9/L$ respectively. 50 mg mirabegron subject #1639-7083 had platelet values of 149, 139, 112, and $135 \times 10^9/L$ on Days 1, 29, 57, and 85 respectively. Mirabegron 100 mg patient #1630-7236 had low platelets at screening and throughout study. Day 1 and Day 90 counts were 128 and $130 \times 10^9/L$ respectively. The nadir value at Day 64 was $106 \times 10^9/L$. Mirabegron subject 2191-7829 had the study drug withdrawn on Day 31 secondary to hypertension (patient also had elevation of liver function tests). On Day 35 her platelet count was $109 \times 10^9/L$ and by Day 63 (22 days after last dose of study drug) it was $280 \times 10^9/L$. There were no other adverse events directly attributable to low platelets.

Reviewers Comment: There is no case of low platelets that I can attribute to mirabegron 50 mg.

Serum Chemistry

Mean changes from baseline to each visit in serum chemistry variables were similar across the treatment groups; mean changes from baseline in all analytes were of small magnitude compared to the normal range of the analyte. No trends in the change from baseline were observed between the mirabegron and placebo groups in these parameters.

No patient had a serum creatinine value that met the PCS criterion (177mmol/L). The incidence of patients whose blood urea nitrogen value met the PCS criterion (12.5mmol/L) was 0.7% (3/436), 0.5% (2/422) and 1.7% (7/419) in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. All of the patients with a blood urea nitrogen value that met the PCS criterion had a history of diabetes, hypertension or renal insufficiency. Most of these patients had evidence of elevation in blood urea nitrogen and/or creatinine prior to starting double-blind study drug. None of these patients had study drug withdrawn due to increased blood urea nitrogen or creatinine.

No patients met laboratory criteria for Hy's Law (i.e., concomitant elevations in ALT and/or $AST > 3$ times the ULN and total bilirubin > 2 times the ULN). The incidence of patients with elevations in ALT, AST, ALP or total bilirubin that met PCS criteria was higher in mirabegron-treated patients than in placebo-treated patients. The overall incidence of hepatic TEAEs was 1.1%, 1.4% and 1.8% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. Most TEAEs were of mild or moderate intensity in all treatment groups. The incidence of mild TEAEs was comparable among placebo-treated and mirabegron-treated patients; moderate TEAEs occurred in mirabegron-treated patients only. Severe TEAEs were reported for 1 patient in the placebo group (ALT increased and GGT increased) and 1 patient in

the mirabegron 50 mg group (ALT increased, AST increased, ALP increased and GGT increased) [see narrative Subject 22528275- Discontinuation].

Table 16: Treatment Emergent Events and Potentially Clinically Significant Hepatic Chemistry Values Study 178-CL-047.

Hepatic Finding, n (%)	Placebo	Mirabegron	
	(n=453)	50 mg (n=442)	100 mg (n=433)
Any Hepatic Finding, n(%)	5 (1.1%)	10 (2.3%)	10 (2.3%)
TEAE Only	1 (0.2%)	2 (0.5%)	1 (0.2%)
Hepatic parameter(s) meeting PCS criteria only	1 (0.2%)	5 (1.1%)	6 (1.4%)
Both TEAE and met PCS Criteria	3 (0.6%)	3 (0.7%)	3 (0.7%)

Source: Table 45, Study Report 178-CL-047, page 153.

Vital Signs

In the overall population, an adjusted mean change from baseline to Week 4 in AM pulse rate of 0.2, 1.0 and 2.2 bpm in patients was observed in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively; these adjusted mean changes were maintained at all subsequent time points. The adjusted mean difference versus placebo in AM pulse rate at the Final Visit was 1.4 and 2.3 bpm for the mirabegron 50 mg and 100 mg groups, respectively. Similarly in the overall population, an adjusted mean change from baseline to week 4 in PM pulse rates of -0.5, 0.9 and 1.9 bpm in patients was observed in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. At week 12, the adjusted mean change from baseline was -1.0, 0.4 and 1.8 bpm in the placebo, mirabegron 50 mg and 100 mg groups, respectively. The adjusted mean difference versus placebo in PM pulse rate at the Final Visit was 1.3 and 2.6 bpm for the mirabegron 50 mg and 100 mg groups, respectively. In the normotensive and hypertensive populations, the observed changes in AM and PM pulse rate were generally similar to those in the overall population.

Pulse rates were analyzed to determine the incidence of tachycardia, defined as any pulse rate ≥ 100 bpm from the AM and PM patient diary data by visit, irrespective of investigator assessment. The incidence of AM tachycardia in the overall population observed at the Final Visit was 0.9%, 1.4% and 1.9% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The incidence of PM tachycardia in the overall population observed at the Final Visit was 2.1%, 1.2% and 1.7% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively.

There appeared to be no significant incidence differences in the normotensive versus hypertensive patients.

Male patients generally had a higher adjusted mean difference from placebo in AM and PM SBP and DBP compared to female patients. In the 50 mg dose group, the adjusted mean increase from placebo in AM and PM pulse rate was greater in patients < 65 years of age than in patients \geq 65 years of age. In the mirabegron 50 mg dose group, the adjusted mean increase from placebo in AM and PM pulse rate was higher in patients < 75 years of age than in patients \geq 75 years of age.

The Sponsor observes that in general these changes did not contribute to greater numbers of TEAEs in mirabegron treated patients. Overall, a small dose-dependent increase in pulse rate was observed in the overall population and subgroups. There is no subgroup that is prone to greater increases in pulse rate changes with mirabegron treatment compared to placebo treatment.

In the overall population and the normotensive population, the mean difference versus placebo at the Final Visit in AM and PM SBP and DBP was generally similar across the treatment groups. In the hypertensive population, the difference from placebo at the Final Visit was numerically higher in the mirabegron 50 mg group compared to the mirabegron 100 mg group.

For normotensive subjects taking 50 mg of mirabegron, the mean AM blood pressure changes from baseline to endpoint compared to placebo were 0.6 mmHg systolic and 0.3 mmHg diastolic. For normotensive subjects taking 50 mg of mirabegron, the mean PM blood pressure changes from baseline to endpoint were 1.1 mmHg systolic and 0.7 mmHg diastolic. For hypertensive subjects taking 50 mg of mirabegron, the mean AM blood pressure changes from baseline to endpoint compared to placebo were 0.7 mmHg systolic and 0.2 mmHg diastolic. For hypertensive subjects taking 50 mg of mirabegron, the mean PM blood pressure changes from baseline to endpoint were 1.8 mmHg systolic and 1.5 mmHg diastolic. (Hypertensive patients are defined as any patient who had a medical history of hypertension and received concurrent antihypertensive medication at the time of the screening visit.)

Table 17: Incidence of AM Systolic Blood Pressure Outliers Study 178-CL-047

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=453	n=442	n=433
Final Visit	AM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		28/433 (6.5%)	Yes (7.5%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		4/381 (1.0%)	Yes (3.4%)	Yes (3.5%)
Change from Baseline ≥ 15 mmHg		0	Yes (0.5%)	Yes (0.3%)
Change from Baseline ≥ 20 mmHg		0	Yes (0.3%)	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		29/378 (7.3%)	Yes (10.8%)	No
Change from Baseline ≥ 15 mmHg		2/398 (0.5%)	Yes (3.0%)	Yes (1.5%)
Change from Baseline ≥ 20 mmHg		2/398 (0.5%)	Yes (1.0%)	Yes (0.8%)
Normotensive Pop		n=292	n=284	n=242
Final Visit	AM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		15/280 (5.4%)	Yes (6.3%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		3/247 (1.2%)	Yes (2.5)	Yes (3.4%)
Change from Baseline ≥ 15 mmHg		0	No	No
Change from Baseline ≥ 20 mmHg		3/247 (1.2%)	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		19/255 (7.5%)	Yes (11.1)	Yes (7.9%)
Change from Baseline ≥ 15 mmHg		0	Yes (2.8%)	Yes (0.5%)
Change from Baseline ≥ 20 mmHg		0	Yes (0.8%)	No
Hypertensive Pop		n=161	n=158	n=191
Final Visit	AM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		13/153 (8.5%)	Yes (9.6%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		1/134 (0.7%)	Yes (5.1%)	Yes (3.6%)
Change from Baseline ≥ 15 mmHg		0	Yes (1.5%)	Yes (0.6%)
Change from Baseline ≥ 20 mmHg		0	Yes (0.7%)	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		10/143 (7.0%)	Yes (10.4%)	No
Change from Baseline ≥ 15 mmHg		2/143 (1.4%)	Yes (3.5%)	Yes (2.8%)
Change from Baseline ≥ 20 mmHg		2/143 (1.4%)	No	Yes (1.7%)

Source: Table 62, Study Report 178-CL-047, page 181

Table 18: Incidence of PM Systolic Blood Pressure Outliers Study 178-CL-047

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=453	n=442	n=433
Final Visit	PM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		27/433 (6.2%)	37/426 (8.7%)	32/412 (7.8%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		10/381 (2.6%)	No	Yes (3.5%)
Change from Baseline ≥ 15 mmHg		3/381 (0.8%)	No	No
Change from Baseline ≥ 20 mmHg		1/381 (0.3%)	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		31/397 (7.8%)	Yes (9.1%)	Yes (9.4%)
Change from Baseline ≥ 15 mmHg		11/397 (2.8%)	No	No
Change from Baseline ≥ 20 mmHg		2/397 (0.5%)	No	No
Normotensive Pop		n=292	n=284	n=242
Final Visit	PM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		12/280 (4.3%)	Yes (7.0%)	Yes (8.3%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		7/247 (2.8%)	No	Yes (4.3%)
Change from Baseline ≥ 15 mmHg		3/247 (1.2%)	No	No
Change from Baseline ≥ 20 mmHg		1/247 (0.4%)	No	Yes (0.5%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		19/255 (7.5%)	No	Yes (9.7%)
Change from Baseline ≥ 15 mmHg		7/255 (2.7%)	No	No
Change from Baseline ≥ 20 mmHg		1/255 (0.4%)	No	Yes (0.5%)
Hypertensive Pop		n=161	n=158	n=191
Final Visit	PM Systolic	Exceeded Placebo Yes/No		
Change from Baseline ≥ 15 mmHg		15/153 (9.8%)	Yes (11.5%)	No (7.1%)
3 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		3/134 (2.2%)	No	Yes (2.4%)
Change from Baseline ≥ 15 mmHg		0	Yes (0.7%)	0
Change from Baseline ≥ 20 mmHg		0	0	0
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg		12/142 (8.5%)	Yes (12.5%)	Yes (9.1%)
Change from Baseline ≥ 15 mmHg		4/142 (2.8%)	No	No
Change from Baseline ≥ 20 mmHg		1/142 (0.7%)	No	No

Source: Table 63, 178-CL-047 Study Report, page 182.

Table 19: Incidence of AM Diastolic Blood Pressure Outliers Study 178-CL-047

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=453	n=442	n=433
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		21/481 (4.4%)	Yes (5.5%)	Yes (4.8%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		29/449 (6.5%)	No	Yes (7.7%)
Change from Baseline \geq 15 mmHg		5/449 (1.1%)	No	Yes (1.6%)
Change from Baseline \geq 20 mmHg		0	0	Yes (0.5%)
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		65/464 (14.0%)	Yes (14.4%)	Yes (15.4%)
Change from Baseline \geq 15 mmHg		14/464 (3.0%)	No	No (2.6%)
Change from Baseline \geq 20 mmHg		2/464 (0.4%)	No	Yes (0.7%)
Normotensive Pop		n=292	n=284	n=242
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10mmHg		13/288 (4.5%)	Yes (6.1%)	Yes (6.3%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		17/270 (6.3%)	No	Yes (8.7%)
Change from Baseline \geq 10 mmHg		3/270 (1.1%)	No	Yes (2.2%)
Change from Baseline \geq 15 mmHg		0	No	Yes (0.7%)
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		37/276 (13.4%)	Yes (16.9%)	Yes (15.8%)
Change from Baseline \geq 10 mmHg		8/276 (2.9%)	No	Yes (3.2%)
Change from Baseline \geq 15 mmHg		1/276 (0.4%)	No	Yes (1.1%)
Hypertensive Pop		n=161	n=158	n=191
Final Visit	AM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		8/193 (4.1%)	Yes (4.3%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		12/179 (6.7%)	No	No
Change from Baseline \geq 10 mmHg		2/179 (1.1%)	Yes (1.3%)	No
Change from Baseline \geq 15 mmHg		0	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		28/188 (14.9%)	No	No
Change from Baseline \geq 10mmHg		6/188 (3.2%)	No	No
Change from Baseline \geq 15 mmHg		1/188 (0.5%)	No	no

Source: Table 64, 178-CL-047 Study Report, page 183.

Table 20: Incidence of PM Diastolic Blood Pressure Outliers Study 178-CL-047

Parameter, n/n (%)		Placebo	Mirabegron 50mg	Mirabegron 100 mg
Overall Population		n=453	n=442	n=433
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		32/433 (7.4%)	Yes (8.5%)	Yes (9.2%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		23/381 (6.0%)	Yes (7.2%)	Yes (8.3%)
Change from Baseline \geq 15 mmHg		4/381 (1.0%)	No	Yes (1.3%)
Change from Baseline \geq 20 mmHg		0	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 10 mmHg		60/397 (15.1%)	Yes (15.6%)	Yes (20.2%)
Change from Baseline \geq 15 mmHg		11/397 (2.8%)	No	Yes (5.1%)
Change from Baseline \geq 20 mmHg		0	Yes (1.0%)	Yes (0.3%)
Normotensive Pop		n=292	n=284	n=242
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10mmHg		16/280 (5.7%)	Yes (6.7%)	Yes (9.1%)
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		17/247 (6.9%)	Yes (8.3%)	Yes (8.7%)
Change from Baseline \geq 10 mmHg		3/247 (1.2%)	Yes (1.3%)	Yes (1.4%)
Change from Baseline \geq 15 mmHg		0	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		41/255 (16.1%)	Yes (16.2%)	Yes (21.8%)
Change from Baseline \geq 10 mmHg		7/255 (2.7%)	No	Yes (4.6%)
Change from Baseline \geq 15 mmHg		0	Yes (1.2%)	Yes (0.5%)
Hypertensive Pop		n=161	n=158	n=191
Final Visit	PM Diastolic		Exceeded Placebo Yes/No	
Change from Baseline \geq 10 mmHg		11/153 (7.2%)	Yes (9.0%)	No
3 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		6/134 (4.5%)	Yes (8.8%)	No
Change from Baseline \geq 10 mmHg		1/134 (0.7%)	No	No
Change from Baseline \geq 15 mmHg		0	No	No
2 Consecutive Postbaseline Visits				
Change from Baseline \geq 5 mmHg		18/143 (12.6%)	No	No
Change from Baseline \geq 10mmHg		5/143 (3.5%)	No	No
Change from Baseline \geq 15 mmHg		0	No	No

Source: Table 64, Study Report 178-CL-047, page 183

Reviewer's Comment: There appears to be a slight increase in 50 mg AM normotensive systolic outliers and 50 mg PM normotensive diastolic outliers (the differences are very small). Three

Patients (2 placebo and 1 mirabegron 100 mg) met the criterion for a PCS change in AM or PM diastolic blood pressure (diastolic blood pressure \geq 105 mm Hg and \geq 15 mm Hg change from baseline to Final Visit). No patients met the criterion for a PCS change in AM or PM systolic blood pressure which were: systolic blood pressure \geq 105 mmHg and \geq 15 mmHg change from baseline to final visit.

ECGs

Mean changes from baseline to the Final Visit in ECG parameters were generally similar across all treatment groups for all parameters except heart rate, RR interval and QTcF [Table 69]. Mean increases in heart rate were 2.9, 3.0 and 5.4 bpm in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. Mean decreases in QTcF were 1.7, 1.9 and 3.0 msec in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. QTcF absolute values > 500 msec were observed for 1 patient (0.2%) in the placebo group only. The incidence of QTcF absolute values > 480 msec and > 450 msec was comparable across all treatment groups. The incidence of a \geq 30 msec increase in QTcF was similar across all treatment groups, and no patients in any treatment group had a \geq 60 msec increase in QTcF.

Table 21: Selected Treatment Emergent ECG Findings During the Double-Blind Treatment Period Study 178-CL-047

Category	Placebo	Mirabegron 50mg	Mirabegron 100mg
Abnormality, n (%)	n=453	n=442	n=433
Patients with baseline and endpoint ECG	403	390	386
Sinus tachycardia	1 (0.2)	1 (0.3)	8 (2.1)
Atrial fibrillation	0	1 (0.3)	0
Supraventricular Atrial Beats	8 (2.0)	5 (1.3)	7(1.8)
Frequent Atrial Premature Complexes (>3)	1 (0.2)	2 (0.5)	1 (0.3)
Ectopic Arrhythmia	0	1 (0.3)	0
ECG changes of Myocardial Infarction	0	1 (0.3) <u>old MI</u>	0
Ventricular Ectopic Beats-multifocal	5 (1.2)	8 (2.1)	5 (1.3)
Frequent ventricular premature complexes (>2)	0	0	2 (0.5)
Prolonged QTc Interval	1 (0.2)	0	1 (0.3)

Source: Table 71, 178-CL-047, page 192

Reviewer's Comment: Two patients were noted to have prolonged QTc in this study: one in the placebo group and one in the mirabegron 100 mg group. The mirabegron 100 mg patient (#1625-7377) who was noted to have a prolonged QT interval had the following ECG results: At Baseline, the QTcF was 443 msec and QTcB was 443 msec (HR=63 bpm). At Day 84 (endpoint), the QTcF was 490 msec and the QTcB was 501 msec (HR=69bpm). The patient suffered no AE as a consequence of this ECG change. No consistent ECG trends are noted. It is notable that mirabegron is recommended as a dose regimen of 25 mg starting and increasing to 50 mg as needed. Mirabegron 100 mg is not a recommended dose.

Post Void Residual

In all treatment groups, baseline mean PVR values were higher in male patients than in female patients. The mean change from baseline to Final Visit was comparable in male and female patients across all treatment groups. In males, the PVR mean change was -2.4 mL (mean Baseline 40.4 mL). In females, the PVR mean change was -3.3 mL (mean Baseline 27.1 mL). In all treatment groups, baseline mean PVR values were lower in patients < 65 years of age compared to patients \geq 65 years of age. Generally, older patients (\geq 65 years of age) showed greater improvement (mean reductions in PVR of 6.6 and 4.9 mL) than younger patients (< 65 years of age) (mean reductions of 0.7 and 1.1 mL) with mirabegron treatment (50 and 100 mg, respectively).

Reviewer's Summary

In this study, the efficacy of mirabegron at doses of 50 and 100 mg once daily for 12 weeks was demonstrated for each of the symptoms of the OAB syndrome, including micturition frequency, incontinence episodes, and volume voided, and their effect on QoL. Both doses of mirabegron were effective in treating these symptoms of OAB at week 4 (the first postdose assessment period) and efficacy was maintained throughout the 12-week treatment period.

The reduction in incontinence episodes per 24 hours noted with treatment with mirabegron 50 and 100 mg (adjusted mean difference versus placebo of -0.34 and -0.50, respectively, at the Final Visit compared to baseline) represents a clinically meaningful improvement. The Sponsor points out that eligibility criteria did not require a minimum number of incontinence episodes at baseline. In patients with incontinence at baseline, the median number of incontinence episodes at baseline was 2.0/day (70% of the FAS were incontinent). This constrains the absolute magnitude of change with treatment in the Sponsor's opinion.

A statistically significant and clinically meaningful reduction in mean number of micturitions per 24 hours from baseline to the Final Visit with treatment with mirabegron 50 mg and 100 mg was also observed (adjusted mean difference from placebo: -0.61 and -0.70, respectively).

Treatment with mirabegron 50 mg and 100 mg resulted in a statistically significant increase compared to placebo in the mean volume voided per micturition (adjusted mean difference from

placebo: 11.1 mL and 11.0 mL, respectively) at the Final Visit. The effects of mirabegron treatment were observed at week 4; both mirabegron groups demonstrated a statistically significant reduction compared to placebo in the mean number of incontinence episodes per 24 hours (adjusted mean difference from placebo: -0.48 and -0.46, mirabegron 50 mg and mirabegron 100 mg) and the mean number of micturitions per 24 hours (adjusted mean difference from placebo: -0.42 and -0.60, mirabegron 50 mg and mirabegron 100 mg).

Overall, 45.2% of all patients experienced 1 or more TEAEs during the study. Two deaths occurred; both deaths were more than 30 days after the last dose of study drug. One death occurred in a patient receiving placebo (cardiovascular death) and the other death was due to metastatic colon cancer (preexisting) in a patient treated with mirabegron 100 mg. A small number of SAEs were reported in patients receiving mirabegron and placebo (2.0, 2.5 and 3.2 % for placebo, mirabegron 50 mg and mirabegron 100 mg respectively). The number of patients discontinuing study drug was similar in the placebo and mirabegron groups.

The overall incidence of AEs reported as hypertension was similar across treatment groups. The Sponsor notes that a definition for hypertension AEs was prespecified in the protocol, which may have led to a higher than expected incidence of these AEs based on the results observed in the phase 2 dose-finding studies. No TEAEs of QTc prolongation and no proarrhythmic events of ventricular tachycardia, ventricular fibrillation or torsade de pointes were observed.

Two patients treated with mirabegron experienced AEs consistent with hypersensitivity, one with lymphocytic vasculitis and purpura (Patient #1815-6541 mirabegron 50 mg), and one with purpura and mild elevations in liver function tests (Patient #2223-6756 mirabegron 100 mg), for which mirabegron could not be excluded as a causative agent.

Acute urinary retention was not observed in mirabegron-treated patients and no mirabegron-treated patients had extremes in PVR that required intervention.

A dose-related increase in pulse rate of 1.4 and 2.3 bpm (AM measures) and 1.3 and 2.6 bpm (PM measures) was observed for the mirabegron 50 and 100 mg groups. One patient in the mirabegron 100 mg group discontinued the study due to an event related to increased heart rate. Females tended to have higher changes in pulse rate than males for the PM measure. In the mirabegron 50 mg group, patients < 65 years of age tended to have higher mean changes in pulse rate compared patients ≥ 65 years of age; for the mirabegron 100 mg dose group, changes were similar between the age groups with a slighter higher change in patients ≥ 65 years of age for the PM measure.

In this study, numerous analyses of blood pressure data revealed a modest effect of mirabegron relative to placebo on mean SBP and DBP. The rate of hypertension-related AEs was similar between mirabegron-treated patients and placebo-treated patients. No consistent trends in ECG changes were identified.

Study 178-CL-047 had an increased of neoplastic adverse events relative to the other 2 pivotal studies. In two instances, cases were reported twice with two different neoplastic preferred terms

(colon cancer and bladder). In no instance, in my opinion, was the time course compatible with mirabegron as causal. There is one possible instance where the Neoplasm Adjudication Committee suggested possible tumor growth stimulation. I do not agree with that suggestion. There is additional discussion of new malignant events in the 12-Week studies in the Integrated Summary of safety shown later in this review.

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

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

This was a phase 3, randomized, parallel group, placebo-controlled, double-blind, multicenter, multinational study conducted in female and male patients of at least 18 years of age with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) present for at least 3 months. This multinational, multicenter study was conducted at 56 sites in Europe and 95 sites in the United States. After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline (visit 2), patients who met inclusion criteria and did not meet exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 25 mg, mirabegron 50 mg or a matching placebo once daily for a 12-week double-blind, placebo-controlled, treatment period that consisted of visits at weeks 4, 8 and 12 with a 2-week follow-up visit after end of treatment.

2201 patients were enrolled and 1306 patients were randomized as follows:

- Full Analysis Set: 1251 patients: placebo: 433 patients; mirabegron 25 mg: 433 patients; mirabegron 50 mg: 440 patients
- Full Analysis Set – Incontinence (reflecting patients with incontinence at baseline): 773 patients: placebo: 262 patients; mirabegron 25 mg: 254 patients; mirabegron 50 mg: 257 patients
- Safety Analysis Set: 1305 patients: placebo: 433 patients; mirabegron 25 mg: 432 patients; mirabegron 50 mg: 440 patients

Study Design: The inclusion/exclusion criteria were the same across the primary studies, except in Study 178-CL-046, where criteria were added to accommodate precautions for the use of tolterodine.

The co-primary efficacy variables included:

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

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

- Change from baseline to end of treatment (final visit) in mean volume voided per micturition
- Change from baseline to week 4 in mean number of incontinence episodes per 24 hours
- Change from baseline to week 4 in mean number of micturitions per 24 hours
- Change from baseline to end of treatment (final visit) in mean level of urgency
- Change from baseline to end of treatment (final visit) in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to end of treatment (final visit) in mean number of urgency episodes (grades 3 or 4 [grade 4 urgency is an urge incontinence episode]) per 24 hours

Safety variables included:

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

Statistical Methods: Since there were 2 co-primary efficacy variables and 6 key secondary efficacy variables, the type I error rate was controlled at the $\alpha = 0.05$ level using a stepwise parallel gatekeeping procedure. At each of the 8 stages, the difference between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to the next stage. The stages and efficacy variables that were evaluated were as follows:

- Stage 1: incontinence episodes at final visit
- Stage 2: micturitions at final visit
- Stage 3: volume voided per micturition at final visit
- Stage 4: incontinence episodes at week 4
- Stage 5: micturitions at week 4
- Stage 6: level of urgency at final visit

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- Stage 7: urgency incontinence episodes at final visit
- Stage 8: urgency episodes (grade 3 or 4) at final visit

Since 2 mirabegron groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the $\alpha = 0.025$ level.

Table 22: Schedule of Assessments Study 178-CL-074

Study Period	Screening	Placebo run-in	Double-blind treatment†			Follow-up	Un-scheduled‡
			4	8	12		
Week	-2	0	4	8	12	14	
Visit	1	2	3	4	5/EoT	6	
Procedures							
Patient information and informed consent	X						
Demographics	X						
Medical history and OAB history	X						
Physical examination	X				X		X
Medication history, OAB treatment history	X						
Cough provocation test (women only)	X						
Inclusion/exclusion criteria check	X	X					
Randomization		X					
Study medication dispensing	X	X	X	X			
Study medication compliance check		X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X
Patient instruction on diary completion, pulse rate and blood pressure measurement	X	X	X	X	X		
Reminder for diary completion before the visit§		X	X	X	X	X	
Diary and questionnaire review with Patient§		X	X	X	X	X	
Safety							
Hematology & biochemistry	X	X	X	X	X		X
Urinalysis¶	X	X	X	X	X		X
Pregnancy test (beta-HCG in serum)††	X				X		X
Vital signs	X	X‡‡	X‡‡	X‡‡	X‡‡	X‡‡	X
Bladder scan (i.e. sonography) (PVR)	X				X		X
12-lead ECG §§	X				X		X
Adverse events	X	X	X	X	X	X	X
Efficacy, Pharmacokinetics and other							
Diary to be completed during 3 consecutive days prior to visit		X	X	X	X		
OAB-q		X	X	X	X		
PPBC, TS-VAS		X			X		
EQ-5D questionnaire		X	X	X	X		
WPAI:SHP		X			X		
CGI¶¶		X			X		
PGI¶¶		X			X		
Data collection on non-study related physician visits for the patient's bladder condition		X	X	X	X		
Blood sampling for population PK †††			X	X	X		

beta-HCG: beta human chorionic gonadotropin; CGI: Clinician Global Impression; ECG: electrocardiogram; EoT: End of Treatment; EQ-5D: European Quality of Life-5 Dimensions; OAB: overactive bladder; OAB-q: Overactive Bladder Questionnaire; PGI: Patient Global Impression; PK: pharmacokinetic; PPBC: Patient Perception of Bladder Condition; PVR: postvoid residual volume; TS-VAS: Treatment Satisfaction Visual Analog Scale; US: United States; UTI: urinary tract infection; WPAI:SHP: Work Productivity and Activity Impairment: Specific Health Problem.

Source: Table 1, page 46, Study 178-CL-074.

Efficacy Results:

Table 23: Co-Primary and Key Secondary Endpoints Study 178-CL-074

Co-Primary Efficacy Results	Mirabegron		
	25mg	50mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr(FAS-I)			
n	254	257	
Adjusted mean difference vs placebo(SE)	-0.40 (0.17) p=0.005	-0.42 (0.17) p=0.001	
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
n	410	426	
Adjusted mean difference vs placebo(SE)	-0.47 (0.18) p=0.007	-0.42 (0.17) p=<0.015	
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
n	410	426	
Adjusted mean difference vs placebo(SE)	4.6 (3.16) p=0.15	12.4 (3.13) p=<0.001	
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
n	254	255	
Adjusted mean difference vs placebo(SE)	-0.34 (0.17) p=0.039	-0.51 (0.17) p=<0.001	
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
n	410	424	
Adjusted mean difference vs placebo(SE)	-0.18 (0.176) p=0.30	-0.37 (0.17) p=0.035	

Source: Table 1, Summary of Clinical Efficacy, page 9. For placebo comparisons see the following 2 tables.

Table 24: Study 178-CL-074 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Placebo	Mirabegron	
		25 mg	50 mg
	(n=262)	(n=254)	(n=257)
Baseline			
Mean (SE)	2.43 (0.145)	2.65 (0.160)	2.51 (0.146)
Final Visit			
Mean (SE)	1.54 (0.151)	1.21 (0.131)	1.13 (0.128)
Change from Baseline			
Mean (SE)	-0.89 (0.159)	-1.36 (0.145)	-1.38 (0.123)
p-Value		0.005	0.001
Superior to placebo at 0.05 level with multiplicity adjustment		Yes	Yes

Source: Table 17, 178-CL-074 Study Report, Page 105

Table 25: Study 178-CL-074 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo	Mirabegron	
		25 mg	50 mg
	(n=415)	(n=410)	(n=426)
Baseline			
Mean (SE)	11.48 (0.142)	11.68 (0.153)	11.66 (0.156)
Final Visit			
Mean (SE)	10.33 (0.166)	10.02 (0.175)	10.04 (0.166)
Change from Baseline			
Mean (SE)	-1.15 (0.139)	-1.66 (0.145)	-1.62 (0.130)
p-Value		0.007	<0.015
Superior to placebo at 0.05 level with multiplicity adjustment		Yes	Yes

Source: Table 18, 178-CL-074 Study Report, page 106

The co-primary efficacy variables were summarized using the FAS and the FAS-I for the following subgroups: sex, age group (< 65, ≥ 65 and < 75, ≥ 75), race and geographical region. Only subgroups which had at least 10 patients in each treatment group were included in the estimation of the subgroup by treatment interaction. Interpretation by the Sponsor of the results of subgroup analyses is limited due to disproportionate numbers of patients in the subgroups for some variables and the influence of sample size on results. There was no statistically significant treatment group by subgroup interaction for sex (P=0.13), age group (P=0.41 for age cut off of

65 years and P=0.77 for the age cut off of 75 years), race (P=0.44) or geographical region (P=0.21) for the change from baseline to final visit in mean number of incontinence episodes per 24 hours. The treatment by sex interaction, while not significant, did reach the P-value < 0.15 (P=0.13) the threshold for further analysis. The findings for mean number of micturitions for 24 hours were similar.

Reviewer’s Efficacy Conclusions: In this study, for both co-primary endpoints mirabegron 25 mg and 50 mg groups (with adjustments for multiplicity) were statistically superior to placebo. Mirabegron 50 mg had a statistically greater increase from baseline to final visit compared to placebo in the mean voided volume while mirabegron 25 mg did not. As a result, subsequent endpoints for mirabegron 50 mg were evaluated at the 0.025 significance level and subsequent endpoints for mirabegron 25 mg were excluded. Mirabegron 50 mg group had a statistically significant greater reduction from baseline to first measured time postdose at week 4 compared to placebo in the mean number of incontinence episodes per 24 hours. However, at Week 8, placebo-subtracted changes from baseline for both primary endpoints were comparable for the 25 mg and 50 mg dose groups. The gatekeeping procedure notwithstanding, the 4 week efficacy for mirabegron 25 mg with respect to incontinence episodes and micturitions per 24 hours at weeks was not statistically significantly different from placebo. However, at 8 weeks they were. At 8 weeks the adjusted mean difference versus placebo for mean number of micturitions per 24 hours for mirabegron 25 mg was -1.53 (p 0.017). At 8 weeks the adjusted mean difference versus placebo for mean number of incontinence episodes per 24 hours for mirabegron 25 mg was -1.38 (p 0.036).

The Sponsor conducted various responder analyses including subjects with a $\geq 50\%$ reduction in daily incontinence episodes:

Table 26: Responder Reduction Incontinence Episodes by $\geq 50\%$ 178-CL-074

	Placebo	Mirabegron	
	(n=262)	25 mg (n=254)	50 mg (n=257)
Responders (n, %)	155 (59.2%)	185 (72.8%)	180 (70.0%)
Difference vs placebo		13.7%	10.8%
95% 2-sided CI		(5.6%, 21.8%)	(2.7%, 19.1%)
p-value		0.001	0.011

Source: Table 26, Study Report 178-CL-074, page 119

The Sponsor also carried out a responder analysis for subjects who had zero episodes of incontinence at endpoint:

Table 27: Subjects with No Incontinence at Endpoint 178-CL-074

	Placebo	Mirabegron	
	(n=262)	25 mg (n=254)	50 mg (n=257)
Responders (n, %)	104 (39.7%)	116 (45.7%)	121 (47.1%)
Difference vs placebo		6.0%	7.4%
95% 2-sided CI		(-2.5%, 14.5%)	(-1.1%, 15.9%)
p-value		0.081	0.057

Source: Table 27, Study Report 178-CL-074, page 120.

Based on the above efficacy results, a consideration of 25 mg versus 50 mg of mirabegron as a potential initial dose was undertaken. This involved consideration of the results of the primary endpoint, the additional secondary endpoints, and the safety data. Notable findings included:

- When the secondary endpoints are considered, mirabegron 50 mg achieved more statistically significant endpoints than mirabegron 25 mg.
- Statistically significant differences from placebo at 4 weeks were not demonstrated for mirabegron 25 mg but were present at Week 8.
- Measures of urgency, which include mean level of urgency, mean number of Grade 3 or 4 urgency episodes and change in baseline of mean level of urgency, all showed a numerical reduction for mirabegron 50 mg and mean level of urgency was also statistically significantly reduced at endpoint as compared to placebo. The 25 mg mirabegron dose was similar to placebo with respect to mean level of urgency. With respect to mean level of urgency and mean number of Grade 3 or 4 urgency episodes, while both mirabegron 25 and 50 mg numerically improved these measures the improvement with mirabegron 50 mg was numerically greater than with the 25 mg dose.
- An urgency responder was defined as a patient with a decrease from baseline to final visit in mean level of urgency which was at least as large as the Sponsor’s proposal for minimally important difference (MID; 0.24). At the final visit, the percentage of responders was greater in the mirabegron 25 mg and 50 mg groups than in placebo. The difference versus placebo was 3.9% for the mirabegron 25 mg group and 8.3% for the mirabegron 50 mg group. The corresponding odds ratio for the mirabegron 25 and 50 mg groups was 1.17 and 1.37, respectively; statistical significance was achieved for the mirabegron 50 mg group.
- In incontinent patients who required pad use, there was a reduction in the mean number of pads used per 24 hours from baseline to final visit; the adjusted mean difference from placebo for the mirabegron 25 mg and 50 mg groups at final visit was 0.16 (more pad use) and -0.17 (less pad use), respectively.
- OAB-q Bother Score: (A negative change in the Symptom Bother score indicated improvement) At the final visit, the adjusted mean difference versus placebo was -1.8 and -2.8 for the mirabegron 25 mg and 50 mg groups, respectively. While the differences

between 50 mg and 25 mg were smaller at Week 8, the reduction from baseline to final visit in the Symptom Bother score was statistically significantly greater in the mirabegron 50 mg group compared to placebo.

- Clinical and Patient Global questions suggest a somewhat better effect of mirabegron 50 mg as compared to mirabegron 25 mg.
- On the WPAI:SHP (Work Productivity and Activity Impairment), a negative change from baseline indicates improvement. Four parameters were assessed: work time missed, impairment while working, overall work impairment and activity impairment. The negative mean change from baseline to week 12 and final visit was greater in the mirabegron 50 mg group compared to placebo for all parameters except overall work impairment.
- Secondary endpoints where no demonstrable differences were noted between mirabegron 25 mg and 50 mg and/or placebo were: nocturia, treatment satisfaction VAS score (both 25 and 50 mg had significant improvement), the Health Related Quality of Life (HRQL), and the EQ-5D. Thus, on some clinically meaningful secondary endpoints, 25 mg performed as well as 50 mg.
- Based on responder analysis, there is a small subset of patients who are responders at the mirabegron 25 mg dose.

Reviewer's Comment: While mirabegron at 4 weeks did not meet the primary efficacy endpoints, it did meet both at 8 weeks. Importantly, there is a subset of patients who are responders at the 25 mg dose at 12 weeks. In addition, some secondary endpoints show comparability between 25 mg and 50 mg. While non-key secondary endpoints seem to favor mirabegron 50 mg, in light of toxicities noted at increased doses of mirabegron (blood pressure, potential risk of neoplasm), it is recommended to start patients on mirabegron 25 mg and titrate them to 50 mg at approximately 8 weeks. Mirabegron 25 mg appears to reach its maximum effect and is comparable to mirabegron 50 mg at 8 weeks. The patients who have a clinical response to mirabegron 25 mg and do not have to titrate upward, may reduce the overall risk of the total population taking mirabegron for adverse events.

Safety:

In their summary of safety results the Sponsor states:

- The overall incidence of TEAEs was similar across the treatment groups (50.1%, 48.6% and 47.3% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively).
- No deaths were reported in this study.
- The overall incidence of treatment-emergent SAEs was 2.8%, 1.6% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

- The overall incidence of patients who discontinued study drug due to a TEAE was 3.7%, 3.9% and 2.5% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

The Sponsor also analyses the safety results with respect to adverse events of interest as follows:

- The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was 8.5%, 12.0% and 11.1% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Although the incidence of hypertension TEAEs was higher in mirabegron 25 mg treated patients relative to the placebo group, adjusted mean changes from baseline to final visit in SBP and DBP were comparable between the two groups.
- No TEAEs of QTc prolongation or its sequelae were observed. No proarrhythmic events of ventricular tachycardia, ventricular fibrillation or torsade de pointes were reported.
- The overall incidence of arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 2.5% in the placebo group and 3.0% in each of the mirabegron groups. Cases of atrial fibrillation of medical importance (*Reviewer's Comment: based on predefined criteria in Appendix 11 of the Cardiovascular Research Report which include a pulse rate > 100 bpm*) were noted in 1 (0.2%) patient treated with placebo, 1 (0.2%) patient treated with mirabegron 25 mg and 2 (0.5%) patients treated with mirabegron 50 mg.
- The overall incidence of adjudicated APTC/MACE cardiovascular events was 0.5% in placebo-treated patients (2 patients experienced nonfatal strokes) and 0.0% in the mirabegron-treated groups.
- There was 1 event of urinary retention in a placebo-treated patient. Acute urinary retention in actively treated patients was not observed in this study.
- The overall incidence of events indicative of potential hypersensitivity was similar across treatment groups. Medical evaluation identified 3 patients (2 placebo, 1 mirabegron 25 mg) with AEs in the category of "likely hypersensitivity". In the placebo patients, these events included dermatitis allergic in 1 patient and rash maculo-papular in the other patient. Rash and rash pruritic were reported in the patient who received mirabegron 25 mg.
- No episodes of syncope were reported in this study.
- No events of seizure were reported in the mirabegron-treated patients; grand mal convulsion and petit mal epilepsy each occurred in 1 patient in the placebo group.
- For hepatic events:
 - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders Comprehensive Search SMQ, was 1.2%, 1.4% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. All hepatic TEAEs, with the exception of 1 event in a patient treated with mirabegron 50 mg, were mild or moderate in intensity. This one patient, judged by the investigator as having a "severe liver test abnormal", had AST and GGT levels slightly above 1 x ULN.
 - No patient met laboratory criteria for Hy's law. The incidence of patients with hepatic parameters meeting PCS criteria was 0.5%, 0.7% and 0.2% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively (excluding patients

that only met the isolated GGT PCS criterion as this laboratory evaluation is nonspecific for hepatic evaluations).

- The incidence of any hepatic finding when TEAEs and PCS hepatic laboratory value criteria were assessed concurrently was 1.6%, 1.6% and 0.9% in the placebo, mirabegron 25 mg and mirabegron 50 mg treatment groups, respectively.

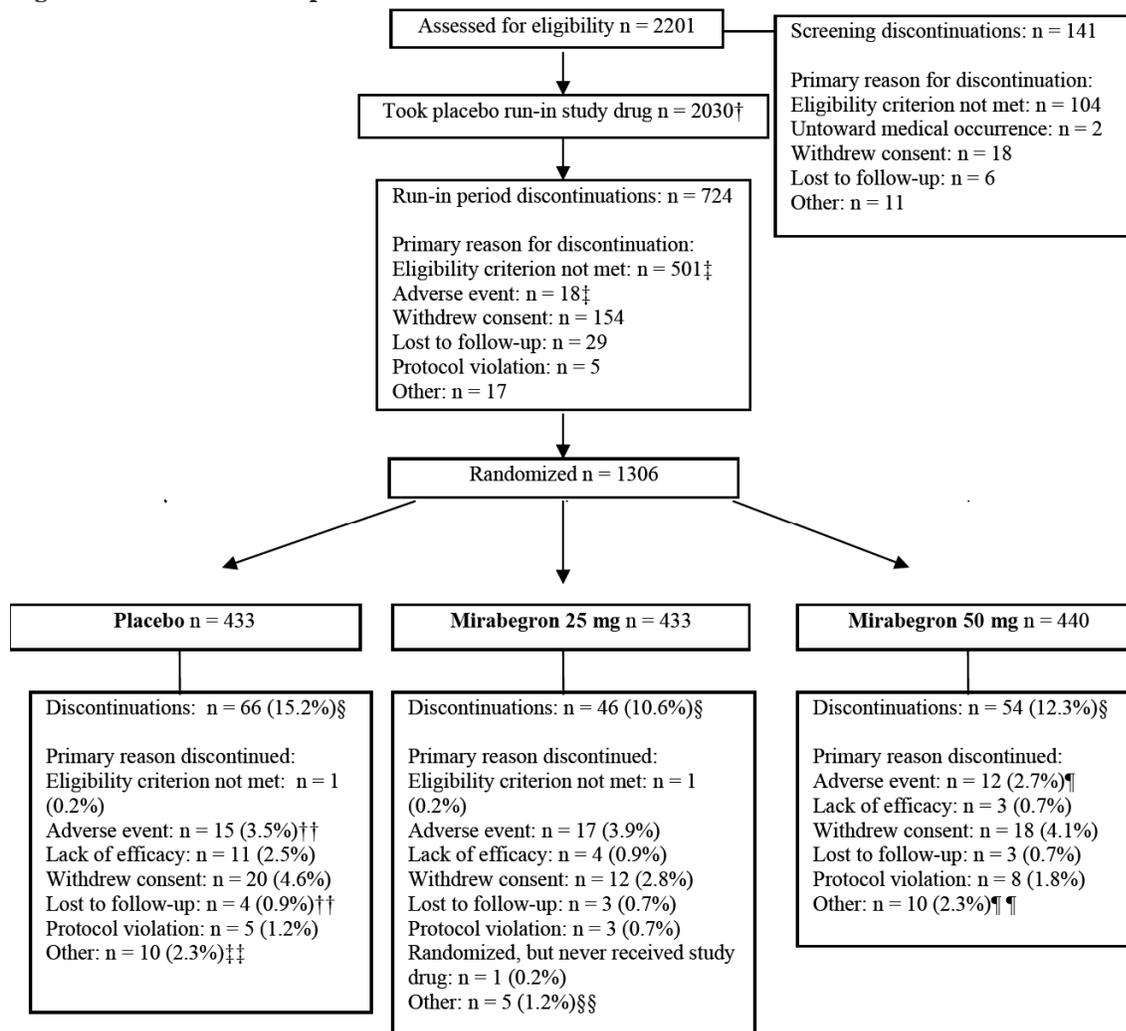
Conclusions relating to chemistry, vital signs and PVR:

- Changes in hematology and serum chemistry parameters, including renal parameters, were unremarkable and consistent across treatment groups.
- For AM measurements, the increases in mean pulse rate with mirabegron 25 mg and 50 mg relative to placebo were not dose-dependent (0.8 and 0.9 bpm, respectively, at final visit) but did appear to be dose dependent for the PM measurement (0.6 and 1.1 bpm, respectively, at the final visit). These increases in pulse rate relative to baseline were not observed at the follow-up visit, at which point study drug had been discontinued for approximately 2 weeks.
- As described above adjusted mean changes from baseline in SBP and DBP measurements were comparable between the placebo and mirabegron 25 mg groups. The mirabegron 50 mg group, however, experienced small increases in SBP relative to placebo (1.5 mm Hg for AM and PM measurements, respectively) and a small increase relative to placebo for AM DBP (1.0 mm Hg). Similar trends were observed in both the normotensive and hypertensive subgroups but the mean increases relative to placebo were smaller in hypertensive patients treated with mirabegron 50 mg. Smaller increases in blood pressure were noted in patients ≥ 65 years of age compared to patients < 65 years of age treated with mirabegron.

Reviewer's Comment: The lack of a blood pressure effect at 25 mg in this study provides support for our recommended starting dose of 25 mg.

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

Figure 4: Subject Disposition Study 178-CL-074



Source: Copy Figure 2, Study Report 178-CL-074, page 78.

Reviewer’s Comment: Reviewer’s Comment: There appear to be no discernible trends noted in patient disposition. Of the 141 patients who discontinued during screening, 104 did not meet eligibility criteria. Of the 724 subjects who discontinued during the Run-in period, 501 did not meet eligibility criteria, 18 experienced an adverse event and 154 withdrew consent. I do not feel that this run-in experience affects the generalizability of the study findings. The percentages of discontinuations during study treatment were low. Subjects lost to followup once randomized were 0.9 % for placebo, 0.7 % for mirabegron 50 mg and 0.7 % for mirabegron 100mg. It is doubtful this incidence will affect trial outcome

Table 28: Overview of Treatment Emergent Adverse Events Study 178-CL-074

Parameter, n (%)	Placebo	Mirabegron	
	(n=433)	25 mg (n=432)	50 mg (n=440)
Adverse Events	217 (50.1)	210 (48.6)	208 (47.3)
Deaths	0	0	0
Serious Adverse Events	12(2.8)	7(1.6)	4 (0.9)
Adverse Events Leading to Study Discontinuation	8 (1.8)	11 (2.5)	6(1.4)

Source: Table 33, Study Report 178-CL-074, page 137.

Reviewer's Comment: SAEs and discontinuations due to AEs were low in Study 074 and comparable between active treatment and placebo.

Table 29: Common (>=2% of Patients in any Treatment Group) Treatment Emergent Adverse Events Study 178-CL-074

MedDRA (v9.1) Preferred Term n (%)	Placebo	Mirabegron	
	(n=433)	25 mg (n=432)	50 mg (n=440)
Hypertension	37 (8.5)	49(11.3)	40(10.7)
Nasopharyngitis	14 (3.2)	15 (3.5)	25 (5.7)
Urinary Tract Infection	10 (2.3)	18 (4.2)	21 (4.8)
Headache	19 (4.4)	9 (2.1)	12 (2.7)
Upper Respiratory Tract Infection	8 (1.8)	9 (2.1)	7 (1.6)
Dry Mouth	9 (2.1)	8 (1.9)	7 (1.6)
Dizziness	2 (0.5)	10 (2.3)	4 (0.9)
Nausea	10 (2.3)	5 (1.2)	6 (1.4)
Back Pain	9 (2.1)	6 (1.4)	4 (0.9)

Source: Table 34, Study Report 178-CL-074, page 138

Reviewer's Comment: Nasopharyngitis and UTI were reported in previous studies as mirabegron-related AEs. In this study, while headache was not apparently mirabegron-related, dizziness was. Hypertension is an AE of interest and is reviewed in a white paper and in the Integrated Summary of Safety. The incidence of hypertension is greater in mirabegron subjects versus placebo which is different than in the other two pivotal studies. This difference is explored below:

Table 30: Summary of Hypertension AEDECOD Terms with Reviewer Analysis Study 178-CL-074.

Hypertension Category	Placebo	Mirabegron 25mg	Mirabegron 50mg
	n=433	n=432	n=440
AEDECOD=hypertension	48	59	61
AETERM indicative of hypertension not qualified as pre-existing	14	26	28
CRF review indicates pre-existing hypertension	11 of 14	23 of 26	24 of 28
Net new onset hypertension	3	3	4
AETERM indicative of worsening hypertension	28	29	33
Worsening hypertension prior to Day 1	2	5	5
Net Worsening Hypertension Day 1 and thereafter	26	24	28

Source: JMP analysis of adae xpt. Dataset 178-CL-074 and reviewer evaluation of CRFs for subjects identified as hypertension not qualified as pre-existing by AETERM.

Reviewer's Comment: 68 subjects were identified by AETERMs indicative of hypertension not qualified as pre existing. The CRFs for these patients were assessed with respect to blood pressure determinations. Blood pressures prior to Day 1 were evaluated for signs of pre-existing hypertension. The first day that blood pressures were determined was not included in the analysis. The presence of hypertension was determined by the criteria of blood pressure exceeding systolic of 140 mmHg or diastolic blood pressure exceeding 90 mmHg. The patient had to have multiple blood pressure determinations on different days to be classified as hypertensive. The blood pressure readings could either be home or office determinations. In their analysis, the Sponsor defined hypertension as an average ≥ 90 mmHg diastolic or ≥ 90 mmHg diastolic on 2 consecutive office visits. It should be noted that the patients selected for further analysis were determined by office visit blood pressure readings. It is therefore possible that some patients who were hypertensive only on home blood pressure determinations would not be included in the analysis. Patients identified with "worsening of hypertension" or related terms did not have their CRFs analyzed.

Based on this limited analysis, there does not appear to be an increased incidence of new onset hypertension in patients receiving mirabegron as compared to placebo. There also does not appear to be an increase of "worsening of hypertension" in patients receiving mirabegron as compared to placebo.

There were no deaths in the study.

Table 31: Serious Treatment Emergent Events Study 178-CL-074

MedDRA (v9.1) System Organ Class Preferred Term n (%) 178-CL-074	Placebo (n=433)	Mirabegron	
		25 mg (n=432)	50 mg (n=440)
Any Serious Adverse Event	12 (2.8)	7 (1.6)	4 (0.9)
Cardiac Disorders	1(0.2)	2 (0.5)	1(0.2)
Atrial Fibrillation	1 (0.2)	0(0.0)	1 (0.2)
Infections and Infestations	1 (0.2)	2 (0.5)	1 (0.2)
Bronchitis Acute	0	0	1 (0.2)
Diverticulitis	0	1 (0.2)	0
Pyelonephritis Acute	0	1 (0.2)	0
Viral Upper Respiratory Tract Infection	1 (0.2)	0	0
Gastrointestinal Disorders	2 (0.5)	1 (0.2)	0
General Disorder and Administrative Site Conditions	1 (0.2)	1 (0.2)	0
Injury Poisoning and Procedural Complications	1 (0.2)	0	1 (0.2)
Radius Fracture	0	0	1 (0.2)
Ligament Rupture	1 (0.2)	0	0
Investigations	1 (0.2)	1 (0.2)	0
Liver Function Test Abnormal	0	0	1 (0.2)
Laparoscopy	1 (0.2)	0	0
Neoplasms Benign and Malignant And Unspecified	0	1 (0.2)	0
Breast Cancer	0	1 (0.2)	0
Psychiatric Disorders	2 (0.5)	0	1 (0.2)
Vascular Disorders	0	1 (0.2)	0
Orthostatic Hypotension	0	1 (0.2)	0
Nervous System Disorders	5 (1.2)	0	0
Surgical and Medical Procedures	1 (0.2)	0	0

The AEs are tabulated by SOC. Preferred terms within SOC are listed based on reviewer's opinion of relevance and if a disproportion on incidence is present.

Source: Table 36, Study Report 178-CL-074, page 140 and Table 12.6.1.6 page 825.

Reviewer's Comment: There were very few SAEs reported in this study, and no single SAE type was reported by more than 1 patient in a treatment group.

Selected Narratives in Brief:

Subject 1534-72081: Atrial Fibrillation: The subject is an 83 year old US white female randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The subject received a total of 29 days of study drug. The study treatment was discontinued due to the adverse event of elevated liver functions and hypokalemia. The events of shortness of breath, elevated liver functions and worsening of rapid atrial fibrillation were considered events of interest.

The medical history included menopause (since 1976), osteoarthritis (since 1990), paroxysmal atrial fibrillation (since 1998), allergy to penicillin (since 1998), hydronephrosis (1998), hypercholesterolemia (since 1998), hypertension (since 1998), hypothyroidism (since 1998-04), ureteropelvic junction obstruction (2000), fatty liver (since 2005-12), periumbilical hernia (2006), moderate osteo-degenerative left knee pain (since 2009), umbilical hernia (2009-10- 01 through 2009-10-16), constipation (since 2009-10-26), and overactive bladder (since 1998). Concomitant medications include: atorvastatin, diltiazem, hydrochlorthiazide, levothyroxine, atenolol, and warfarin.

On day 24, an adverse event of shortness of breath was reported. No concomitant medications were given and no changes were made to study drug due to this adverse event. On day 36, the adverse event of shortness of breath was reported as resolved. On day 27, adverse events of abnormal liver function and hypokalemia were reported. The subject was given potassium orally for a total daily dose of 20 mEq on day 34 and 40 mEq on day 35 for the indication of hypokalemia. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. On day 27, the subject had a potassium level of 3.2 mmol/L and the subject's AST and GGT were slightly elevated. On day 29, study drug was discontinued due to the adverse event of abnormal liver function. On day 27, adverse events of abnormal liver function and hypokalemia were reported. The subject was given potassium orally for a total daily dose of 20 mEq on day 34 and 40 mEq on day 35 for the indication of hypokalemia. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. On day 34, the adverse event of abnormal liver function was reported as resolved and on day 35, the adverse event of hypokalemia was reported as resolved.

Study Day	Alanine Aminotransferase (ALT) (normal range 1 - 30 U/L)	Aspartate Aminotransferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 20.3 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 - 32 U/L)	Potassium (normal range 3.7 - 5.4 mmol/L)
-15	12	19	82	6.7	25	3.7
-1	14	21	84	3.8	30	4.2
27	28	35	86	6.7	43	3.2
34	22	26	89	10.3	45	3.9

Source: Subject Narrative

On day 34, a serious adverse event of worsening of rapid atrial fibrillation was reported. The subject had a previous medical history of paroxysmal atrial fibrillation and was taking warfarin

orally for a total daily dose of 2.5 mg and diltiazem orally for a total daily dose of 120 mg prior to screening for the trial. On day 34, physical examination findings during a study visit showed changes that were considered clinically significant. ECG findings showed atrial fibrillation with rapid ventricular response. The subject was extremely short of breath and was pale. The subject was also assessed to have a rapid heart beat therefore, was transported to the emergency department (ED). Upon admission to the ED, the subject had no chest pain, nausea, vomiting, presyncope or diaphoresis. An electrocardiogram showed atrial fibrillation and the native QRS was narrow with intermittent wide complex. There was a run of wide complex rhythm at a rate of approximately 150 bpm, which may have been either supraventricular tachycardia (SVT) with aberration due to her history of left bundle branch block or ventricular tachycardia. The subject was treated with diltiazem hydrochloride intravenous (IV) drip at a total daily dose of 10 mg and with metoprolol tartrate IV drip at an unknown dose. After receiving the diltiazem hydrochloride, the subject's heart rate decreased into the 80s. Upon further questioning, it was noted that just prior to the event of worsening atrial fibrillation, the subject neglected to take her cardiac medications for 2 days since "she felt that she did not require this ongoing medication because she felt well." The subject was admitted to the hospital and oral medications were restarted. Laboratory testing during hospitalization revealed creatine phosphokinase (CK) of 80 U/L, creatine phosphokinase MB (CK-MB) of 0.7 ng/ml, and troponin of < 0.012 ng/ml. On day 35, the subject was successfully electrically cardio-converted and returned to a normal sinus rhythm, and her hemoglobin was 12.7, potassium 3.9 and creatinine 1.06. Cardiac enzymes were negative and chest x-ray showed no active disease. On day 36, the serious adverse event of worsening rapid atrial fibrillation was resolved and the subject was discharged from the hospital in stable condition.

Reviewer's Comment: The patient has a past history of atrial fibrillation and prior to the acute event did not take her cardiac medications for 2 days. In addition study drug had been stopped 5 days prior to acute event. I cannot assign causality to mirabegron.

Subject 3221-71482: Radius Fracture: The subject is a 67 year old white Norwegian female randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. Her history included menopause (since 1992), stress urinary incontinence (2003-09-09), chronic obstructive airways disease (since 2007). Her concomitant medications included budesonide/formoterol, acetyl cysteine, tiotropium and estradiol. On day 45, a serious adverse event of fracture of the right radius was reported. The subject suffered a radial fracture after falling off a chair while cleaning a window. There was no report of dizziness or other symptoms prior to the fall. The subject was successfully treated with surgery on day 49. Study drug was interrupted due to this serious adverse event and was restarted on day 50. The event was reported as resolved on day 49. The investigator considered this serious adverse event of fracture of the right radius to be moderate and not related to study drug.

Reviewer's Comment: There is no indication of obtundation, diminished attention, or balance problem. There is no evidence from which attribution to mirabegron could be suggested.

Subject 1630-70462: Elevated Liver Function Tests: The subject is a 57 year old black US male randomized to mirabegron 25 mg on 29 July 2009. The study treatment was discontinued due to the adverse event of elevated LFTs on day 63. The medical history included absent left testis (since 1951-12-23), tonsillectomy (1970-06), marijuana use (1971 through 1983), methamphetamine use (1971 through 1979), reconstruction of nasal/orbital bones (1972), intermittent headaches (since 1980), cocaine use (1986 through 1989), hypertension (since 2006), investigated benign hematuria (since 2006), hepatitis A (since 2009), hepatitis B (since 2009), hepatitis C (since 2009), elevated creatinine (since 2009-07-14), inverted T waves (since 2009-07-14), left anterior hemiblock (since 2009-07-14), and overactive bladder (since 2007). Concomitant medications include atenolol and acetaminophen.

On day 30, the subject's LFTs were increased, but the investigator noted that it was a hot day and the subject was dehydrated. On day 57, the subject's LFTs were further elevated. Hepatitis B core antibody (ANTI-HBc), hepatitis A virus antibody (ANTI-HAV), and hepatitis C antibody (ANTI-HCV) were all positive. The subject denied recent alcohol or drug abuse, however medical history included substance abuse. The subject was asymptomatic. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. It was unknown whether or not the LFTs were fluctuating prior to therapy with study drug. The investigator stated that he believed that prior to starting the study, the screening serology results were positive for hepatitis. Study drug was discontinued on Day 63 due to the adverse event of elevated LFTs. The serious adverse event of elevated LFTs was reported as ongoing at the time of study completion (Day 92) and no additional laboratory results were available after Day 92.

Study Day	Alanine Amino-transferase (ALT) (normal range 1 – 39 U/L)	Aspartate Amino-transferase (AST) (normal range 1 - 39 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 20.3 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 10 - 49 U/L)	Eosinophils (normal range 0 - 480 x 10 ⁶ /L)
-15	48	29	118	8.7	48	330
1	44	28	126	6.8	44	290
30	201	102	112	9.4	54	420
57	473	242	133	7	169	500
65	361	134	139	8.2	167	340
65	365	135	138	8.6	167	330
79	166	70	128	8.6	135	not tested
92	123	65	150	7.2	95	not tested

Source: Patient narrative

Reviewer's Comment: The subject's medical history of hepatitis A, hepatitis B, and hepatitis C are likely alternative etiologies for this event.. However, a role of mirabegron in the event cannot be excluded.

Subject 3191-71351: Breast Cancer: The subject is a 63 year old white Finnish female randomized to mirabegron 25 mg on [REDACTED] (b) (6). The medical history included right hip congenital dislocation (since 1946-04-12), hypermenorrhea (1983-11-25 through 1985-09-30), hysterectomy (1985-09- 30), right hip total endoprosthesis (1992-12-08), primary arthritis of left

hip (1995-12-22 through 2002-04-17), gastro-esophageal reflux disease with esophagitis (since 1999), left hip total endoprosthesis operation (2002-04-17 through 2002-09-17), tinnitus auris (2002-09 through 2003-12), carpal tunnel syndrome operation at left hand (2003-02-18) and at right hand (2004-01-15), hypertension (since 2006), alopecia areata (since 2007-11-02), acetylsalicylic acid allergy (since 2007-11-02), colophony allergy (since 2007-11-02), rectocele operation (2007-11-30), non-insulin-dependent diabetes mellitus (since 2008-05), cramps in lower extremity (since 2009-08), and left shoulder pain radiating to left breast (since 2009-10-01). Concomitant medications include: solifenacin, esomeprazole, codeine/paracetamol, ramipril, metformin, calcium carbonate and vitamin B-12 NOS.

On day 8, a serious adverse event of breast cancer was reported. This subject had a relevant medical history that included left shoulder pain that radiated to her left breast since day -27 (b) (6). On day 8, a biopsy of the left breast was taken and showed severe lobular carcinoma. Study drug was discontinued on day 17. At the time of study completion, the serious adverse event of breast cancer was reported as not resolved. Additional information sought by the Sponsor revealed a history of tobacco use and use of hormonal treatments was unknown. The information did confirm that the subject had presented with left shoulder pain radiating to the left breast beginning on day -27 (b) (6). The pathology report noted the needle biopsies consisted almost entirely of tumor tissue in uniform cell layers. The report noted the invasive carcinoma was more likely to be lobular cancer than ductal; however, additional information in the query response described the cancer as ductal and lobular cancer of the breast. The subject underwent surgery to remove the breast on day 49 (b) (6). The breast cancer was classified as T2N1. The subject reportedly received cytostatic treatment and radiation therapy following the surgery. No additional information was available for this case.

Reviewer's Comment: The subject experienced an adverse event of breast cancer on Day 8 with confirmed evidence of invasive breast cancer with lymph node metastases, adjudicated by the Neoplasm Adjudication Committee as malignant with definite evidence based on biopsy results. The subject had pain in the shoulder radiating to the breast for a month which led to the biopsy. The malignancy status of the breast cancer was confirmed by biopsy as malignant. A causal association between the event of breast cancer and mirabegron was not reasonable based on presence of pain symptoms which preceded first dose of study medication and an incompatible timeline (invasive breast cancer with metastases reported on day 8, suggesting that the underlying pathology was ongoing prior to study treatment initiation).

Subject 1624-70017: Diverticulitis: The subject is a 44 year old white US male randomized to mirabegron 25 mg on (b) (6). The subject received a total of 83 days of study drug. The study treatment was not discontinued due to the adverse event. The medical history included myopia (since 1975) and granulomatous disease (since 2009) {site not specified in CRF but possibly gastro-intestinal}. The patient was receiving no concomitant medications.

On Day 68, a serious adverse event of diverticulitis was reported and the subject was admitted to the hospital. The subject had a relevant medical history of granulomatous disease. The subject presented to the emergency room with a 3-day history of bilateral lower quadrant abdominal

pain, mild diarrhea, vomiting and fevers. The subject was hypertensive and tachycardiac. The white blood cell count was 11.9 (units and normal range not provided). A computed tomography (CT) scan revealed findings compatible with acute diverticulitis of the proximal sigmoid colon, with tiny microperforation and no evidence of resulting abscess, and with a few small foci of extraluminal air near the sigmoid colon. The subject's abdominal pain was reported as resolved on Day 69. The white blood cell count increased to 12.8 (units and normal range not provided) on Day 69 before decreasing to 8.0 on Day 70.

Reviewer's Comment: While the narrative attributes the above event to diverticulitis it is possible that the patient's granulomatous disease could have also played a role. Taking that fact into consideration does not make it possible for me to attribute a causal role for mirabegron in this SAE.

Within the EU/NA Long-term study, 3/812 (0.4%) 50 mg patients, 6/820(0.6%) and 2/812(0.2%) patients mirabegron 100 mg patients reported an SAE in the Musculoskeletal and Connective Tissue Disorders SOC. In the 50 mg group, all three SAEs were osteoarthritis. In the 100 mg group, the SAEs were lumbar spinal stenosis, ligament rupture, tenosynovitis, rotator cuff syndrome and muscle injury. The overall incidence of musculoskeletal disorders in the 12 Weeks studies was not increased in mirabegron subjects over placebo subjects. The incidence of musculoskeletal disorders in the EU/NA Long-term study was 1.2% in the mirabegron 50 mg group, 0.6% in the mirabegron 100 mg group and 0.2% in the tolterodine group. Arthralgia, muscle spasms, muscular weakness and musculoskeletal chest pain was reported in two or more mirabegron patients. Only musculoskeletal chest pain was reported in two or more mirabegron 50 mg patients.

Reviewer's Comment: The Musculoskeletal and Connective Tissue Disorders SOC SAEs in the EU/NA Long-term study are diverse lesions with the exception of osteoarthritis, and it is not plausible that mirabegron could be associated with osteoarthritis which usually develops over many years. This safety issue is resolved. There is no new safety concern.

Reviewer's Comment: No particular safety concern or signal is discerned in the SAEs for Study 178-CL-074.

Table 32: Treatment Emergent Adverse Events Leading to Permanent Study Discontinuation Study 178-CL-074

MedDRA (v9.1) System Organ Class Preferred Term n (%) 178-CL-074	Placebo (n=433)	Mirabegron	
		25 mg (n=432)	50 mg (n=440)
Any Serious Adverse Event	16 (3.7)	17 (3.9)	11 (2.5)
Gastrointestinal Disorders	5 (1.2)	3 (0.7)	3 (0.7)
General Disorders and Administrative Site Conditions	2 (0.2)	3 (0.7)	2 (0.5)
Chest Pain	1(0.2)	1(0.2)	0
Feeling Abnormal	0	1(0.2)	0
Irritability	0	1(0.2)	0
Malaise	1(0.2)	0	1(0.2)
Pyrexia		0	1(0.2)
Investigations	0	3 (0.7)	2 (0.5)
Liver Function Test Abnormal	0	1(0.2)	2 (0.5)
Blood Glucose Increased	0	1(0.2)	0
Blood Lactate Dehydrogenase Increased	0	0	1(0.2)
Gamma-glutamyl Transferase Increased	0	0	1(0.2)
Weight Increased	0	1(0.2)	0
Nervous System Disorders	6 (1.4)	2 (0.5)	3 (0.7)
Headache	4 (0.9)	0	3 (0.7)
Dizziness	1 (0.2)	0	3 (0.7)
Cardiac Disorders	2 (0.5)	2 (0.5)	1 (0.2)
Myocardial Ischemia	0	0	1(0.2)
Palpitations	1(0.2)	1(0.2)	0
Tachycardia	0	1(0.2)	0
Atrial Fibrillation	1(0.2)	0	0
Musculoskeletal and Connective Tissue Disorders	1(0.2)	2 (0.5)	1(0.2)
Infections and Infestations	1(0.2)	0	2 (0.5)
Skin and Subcutaneous Tissue Disorders	1(0.2)	2 (0.5)	0
Rash	0	2 (0.5)	0
Rash Pruritic	0	1(0.2)	0
Skin Discoloration	0	1(0.2)	0
Dermatitis Allergic	1(0.2)	1(0.2)	0
Injury, Poisoning and Procedural Complications	0	1(0.2)	0
Skin Laceration	0	1(0.2)	0
Metabolism and Nutrition	1(0.2)	0	1(0.2)

Disorders			
Hypokalemia	0	0	1(0.2)
Neoplasms Benign and Malignant	0	1(0.2)	0
Breast Cancer	0	1(0.2)	0
Psychiatric Disorders	2 (0.5)	1(0.2)	0
Renal and Urinary Disorders	0	1 (0.2)	0
Bladder Pain	0	1(0.2)	0
Stranguria	0	1(0.2)	0
Urethral Pain	0	1(0.2)	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	1(0.2)
Pulmonary Fibrosis	0	0	1(0.2)
Ear and Labyrinth Disorders	2 (0.5)	0	0

The AEs are tabulated by SOC. Preferred terms within SOC are listed based on reviewer's opinion of relevance and if a disproportion on incidence is present.

Source: Table 38, Study Report 178-CL-074, page 144.

Reviewer's Comment: There were few AEs leading to discontinuation and only "headache", "dizziness" and "rash" were reported by more than 1 subject in a treatment group.

Narratives in Brief:

Subject 0047-72204: Palpitations: The Subject is a 52 year old white US female randomized to mirabegron 25 mg 8 December 2009. The subject received a total of 17 days of study drug. The study treatment was discontinued due to the adverse events of nausea, nervousness and palpitations on day 17. The medical history included allergies: dust, mold, and pollen (since 1962), asthma (since 1962), allergies: sulfa, penicillin (since 1980), allergy to IVP dye/ causing rapid pulse and shock (since 1980), irritable bowel syndrome (since 1983), hypothyroidism (since 1992), chronic cystitis (1992 through 2007-05-17), fibromyalgia (since 1992), thyroidectomy (1992), gastroesophageal reflux disease (since 1993), diabetes (since 2003), hypertension (since 2004), endometriosis (2005 through 2005-06-08), fibroids (2005 through 2005-06-08), sleep apnea (since 2005), hysterectomy (2005-06-08), Burch urethropexy (2005-06-20), back pain (since 2006), dizziness (since 2006), hypercholesterolemia (since 2006), migraine (since 2006), nausea (since 2006), palpitations (since 2006), lumbar, cervical and thoracic disc herniation (since 2006-07-05), depression (since 2008), and overactive bladder (since 1982).

Her concomitant medications include: levothyroxine, fluticasone/salmeterol, albuterol, ibuprofen, metformin, oxycodone, acetaminophen, ramipril, atorvastatin, nifedipine, duloxetine, and omeprazole.

On day 16, adverse events of nausea, nervousness and palpitations were reported. The subject was taking dimenhydrinate prior to baseline for the indication of nausea. Dimenhydrinate was considered a prohibited medication, therefore was not taken during study conduct. On day 16, the subject took dextrose/ levulose/ phosphoric acid orally at a total daily dose of 5 ml for the indication of nausea. No vital sign data or laboratory results were available for day 16. On day 17, study drug was discontinued due to the adverse events and adverse events of nausea, nervousness and palpitations were reported as resolved on this same date. There are no vital signs or ECGs on the day of the event.

Reviewer's Comment: This subject with a history of irritable bowel syndrome, fibromyalgia, depression, endometriosis, nausea and palpitations, experienced nausea, nervousness, and palpitations after 16 days of mirabegron 25 mg treatment. The patient was taking dimenhydrinate for nausea which was a prohibited medication during the trial. The subjects' symptoms were reported to resolve on the same day as mirabegron discontinuation. Although the subject had been chronically taking levothyroxine as well as albuterol which may cause symptoms of sympathetic overstimulation such as nausea, nervousness, and palpitations, due to compatible timelines, causal association between the events and mirabegron cannot be excluded with the patients' nausea, nervousness and palpitations.

Subject 3132-71820: Tachycardia: Dizziness, Irritability: The subject is a 34 year old white Hungarian female randomized to mirabegron 25 mg on 24 November 2009. There is no relevant past medical history. Her concomitant medication is desogestrel/ethinylestradiol oral contraceptive.

On day 1, adverse events of dizziness, irritability and tachycardia were reported. No concomitant medications were given for the indication of events of dizziness, irritability and tachycardia. The subject had a previous adverse event reported of tachycardia that began and ended on day -4. The study drug was discontinued on Day 28. On day 116, the events of dizziness, irritability and tachycardia were reported as resolved. The investigator considered the events of dizziness, irritability and tachycardia to be moderate and possibly related to study drug. Between day 1 and day 116, multiple episodes of heart rates over 100 bpm were reported. The subject's highest reported heart rate was 109 bpm in the morning on day 28 and the lowest reported heart rate was 72 bpm in the morning on day 28. During the screening period, the subject's heart rate was 106 bpm on day -4. The subject's heart rate was elevated at the follow up visit (day 116).

ECG Findings

Study Day	HR Mean (bpm)	PR Mean (ms)	QRS Duration (ms)	RR Mean (ms)	QTCF Mean (ms)	QTCB Mean (ms)	QT Mean (ms)	ECG Interpretation
-15	95	126	78	633	412	444	353	normal
28	86	105	89	700	381	405	339	normal

Vital Signs

Clinical Review

{Insert Reviewer Name}

{Insert Application Type and Number}

{Insert Product Trade and Generic Name}

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	106/72	92
Baseline: Office Device	110/74	92
Week 4 / Final Visit: Home Device	122/80	101
Week 4 / Final Visit: Office Device	127/73	91
Follow-Up Visit: Home Device	121/78	96
Follow-Up Visit: Office Device	124/77	105

Source: Patient Narrative

Reviewer's Comment: The patient's heart rate was elevated prior to exposure to the study drug, and the patient had an AE of tachycardia during the run-in period. The heart rate also remained elevated after the study drug was stopped on Day 28. On Day 116, despite the observation that the heart rate was elevated on Day 116, the events of dizziness, irritability and tachycardia are reported as resolved. It still remains possible that mirabegron could be causally related to these events but interpretation is confounded by tachycardia prior to drug exposure and lack of clear de-challenge.

Subject 1630-71016: Rash Pruritic: The subject is a 66 year old white US female randomized to mirabegron 25 mg on 23 September 2009. She received a total of 37 days of drug which was discontinued due to the adverse events of rash over entire trunk and inner thighs and itching from abdominal rash.

The medical history included menopause (since 1994), uterine polyps cauterized (1999), osteoporosis (since 2004), left shoulder fracture (2005), dislocated left shoulder (since 2005-11), left radial nerve damage (since 2005-11), minimal ulnar nerve damage in left pinky finger (since 2005-11), fibroids (since 2005-12-22), investigated hematuria- negative (2006-10), hypercholesterolemia (2007-08-10 through 2007-12), GERD (2008-03), right knee arthralgia (2008-04-05 through 2008-06-09), intermittent monilial vulvovaginitis (since 2008-05-19), hypertension (since 2008-12), mild cataracts, bilateral (since 2009-03-16), and overactive bladder (since 2006). Concomitant medications include: vitamins, calcium supplements, acetylsalicylic acid, and hydrochlorothiazide.

On day 37, adverse events of rash over entire trunk and inner thigh and itching from abdominal rash (pruritic) were reported. The subject was given diphenhydramine orally for a total daily dose of 25 mg as needed for the indication of itching from rash. This rash was described as a macular rash with erythema, beginning on the abdomen and spreading to rest of the trunk and inner thighs. Pertinent negatives included no constitutional symptoms, eosinophilia or elevations in liver chemistries. The platelet count was not altered. On day 40, the adverse event of itching from abdominal rash was reported as resolved and on day 43, the adverse event of rash was reported as resolved. Skin findings were considered normal during the end of treatment by physical examination (day 49).

Reviewer's Comment: While it is possible that this event was a delayed reaction to multiple medications the patient was using, in light of the positive dechallenge,

a causal association of this hypersensitivity reaction to mirabegron cannot be ruled out.

Subject 1645-70556: Skin Laceration: The subject is a 49 year old white US male randomized to mirabegron 25 mg 12 August 2009. The study treatment was discontinued due to the adverse event of left lower leg laceration on day 53. The medical history included chronic tinnitus (since 1975), cystic acne (since 1975), GERD (since 1997), erectile dysfunction (since 2001), anxiety (since 2004), depression (since 2004), fatigue (since 2004-06-01), cervical arthritis (since 2006-10), bilateral leg numbness (since 2007), chronic lower back pain (since 2007), herniated disc (since 2007), migraines (since 2007), history of bronchitis (2007-08-21 through 2007-09), BPH (since 2008), dizziness (2008-12-10 through 2008-12-14), environmental allergies (since 2008-12-12), sleep apnea (since 2009-04), sebaceous cyst removal of right posterior neck (2009-07-08), and obesity (since 2009-07-15). Concomitant medications include lansoprazole, sildenafil, ibuprofen, hydrocodone/acetaminophen, loratadine, lorazepam and tamsulosin.

On day 53, an adverse event of left lower leg laceration was reported. No additional information regarding this leg laceration or the events associated with the leg laceration were reported. Study drug was withdrawn due to the adverse event of left lower leg laceration. This adverse event was reported as not resolved at the time of study completion. Additional adverse events reported for this subject included tachycardia (day -5 through day 29), increased fatigue (day 29 and ongoing that the time of study completion), and abdominal pain (day 29 through day 30).

Reviewer's Comment: Additional information was sought from Sponsor as to the circumstances of the injury. The patient is reported as having fatigue as a background condition and reported fatigue from Day 29. The patient was also taking lorazepam and hydrocodone/acetaminophen. In a 9 December 2011 response to information request for additional detail about the patient's state concentration and attention at the time of the event, the Sponsor stated that no additional information is available. I cannot attribute the event of skin laceration in this case to mirabegron.

Subject 3191-71351: Breast Cancer: Mirabegron 25 mg. See narrative under Serious Adverse Events.

Subject 1667-70310: Hypertension: The subject is a 69 year old US female of Asian descent who was randomized to mirabegron 25 mg on 14 July 2009. The subject received a total of 29 days of study drug. The study treatment was discontinued due to the adverse event of worsening hypertension on day 30 (2009-08-12). The patient's medical history includes hyperlipidemia (since 2002), diabetes mellitus type II (since 2002), hypertension (since 2002), gout (since 2004) and cardiomegaly (since 21 January 2009). Her current medications include valsartan, amlodipine, metformin, pioglitazone, and simvastatin. On day 30, an adverse event of worsening of hypertension was reported. On that day, the subject's systolic blood pressures per the subject diary were in the 190's throughout the day and the subject was started on hydrochlorothiazide orally for a total daily dose of 25 mg and amlodipine orally for a total daily dose of 10 mg for the indication of hypertension. Vital sign averages are below:

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	141/76	56
Baseline: Office Device	149/73	61
Week 4 / Final Visit: Home Device	191/85	59
Week 4 / Final Visit: Office Device	191/84	61
Follow-Up Visit: Home Device	132/62	62
Follow-Up Visit: Office Device	121/60	60

Source: 1667-70310 patient narrative

According to the CRF, the highest blood pressure readings on Day -17 were systolic 156 mmHg and diastolic 88 mmHg. The blood pressure readings on Days -5, -4, -3, -2, and -1 were lower. The blood pressure ranges during this time period were 123-167 mmHg systolic and 61-83 mmHg diastolic.

Reviewer's Comment: Although the patient had well documented hypertension at baseline, lacking an alternative etiology, a causal association of mirabegron and this case of an increase in pre-existing hypertension cannot be ruled out.

Subject 2038-70286: Exacerbation of Hypertension: The subject is a 72 year old white/Hispanic US male randomized to mirabegron 25 mg 16 July 2009. The subject received 30 days of study drug discontinuing 2 days after the adverse event of exacerbation of hypertension occurred. The patient's medical history includes hypertension since 1 June 2009. The patient was taking terazosin 10 mg daily for benign prostatic hypertrophy. On day 28, as per patient diary, the highest systolic blood pressure was 132 mmHg and the highest diastolic blood pressure was 95 mmHg. The patient was treated with citalopram with resolution of the blood pressure elevation by Day 30. On Day 46 the blood pressure was systolic 144 mmHg and diastolic 106 mmHg. Vital sign averages are below:

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	130/92	63
Baseline: Office Device	130/91	64
Week 4: Home Device	128/91	65
Week 4: Office Device	132/94	64
Final Visit: Home Device	108/85	97
Final Visit: Office Device	107/75	96
Follow-Up Visit: Home Device	129/86	59
Follow-Up Visit: Office Device	131/83	54

Source: 2038-70286 patient narrative

According to the CRF, on Day -21, the highest systolic blood pressure was 128 mmHg and the highest diastolic blood pressure was 85 mmHg. The range of blood pressures for Days -6, -5, -4, -3, -2, and -1 were 116-145 mmHg for systolic and 82-96 mmHg for diastolic.

Reviewer's Comment: Patient entered study with hypertension, not well controlled, with notably high diastolic BPs (ranging up to 96 mm Hg). On the day of the adverse event the diastolic blood pressure was higher than on other days. Increase in the blood pressure related to mirabegron cannot be ruled out.

Subject 3225-71561: Pulmonary Fibrosis: Subject is a 61 year old white Norwegian female randomized to mirabegron 50 mg on 7 November 2009. The subject received 54 days of study drug. The study treatment was discontinued due to the adverse event of fibrosis of lungs on Day 54. The patient's medical history includes Scheuerman's disease (kyphosis), fibromyalgia, osteoarthritis, lumbar osteoporosis, and seasonal rhinitis. Her concomitant medications include: estradiol, caffeine/phenazone, calcium carbonate/cholecalciferol and ibuprofen. The subject experienced the adverse event of pneumonia from Day 3 to Day 27. She was diagnosed with pulmonary fibrosis on Day 28. A cough was reported on Day 34. The Sponsor states that etiologies could include the preceding pneumonia or drug hypersensitivity. On Day -18 and Day-1 the eosinophil counts were 60 and 190 x 10⁶/L (NI range 0 - 480 x 10⁶/L) respectively. On 16 November 2009, the patient began topical steroidal treatment for eczema. On Day 27 the eosinophil count was 340. There are no radiographic reports in the CRF.

Reviewer's Comment: Assigning causality to mirabegron is confounded by the pneumonia which can cause pulmonary fibrosis.

Subject 1534-72081: Abnormal Liver Function Test: Mirabegron 50 mg. See narrative under SAEs. Atrial Fibrillation and Hypokalemia.

Subject 2053-7047: Abnormal Liver Function Tests: Subject is a 72 year old white US female randomized to mirabegron 50 mg on 27 August 2009. The subject received a total of 56 days of study drug. The study treatment was discontinued due to the adverse events of elevated AST, elevated ALT, elevated LDH, and elevated GGT on day 56 (2009-10-21). The last visit occurred on day 86. Medical history included allergies to adhesives, penicillin and seasonal allergies (since 1980), menopause (since 1986), cataract repair (1990), shortness of breath with exertion (since 1990), left knee injury (since 1993), benign bladder polyp (2000), hypercholesterolemia (since 2002), hypertension (since 2002), osteopenia (since 2004), GERD (since 2005), blind in left eye (since 2005-05), and carpal tunnel left arm (since 2008-02). Concomitant medications include: chondroitin sulfate/glucosamine, calcium citrate, acetylsalicylic acid, atenolol, hydrochlorothiazide, simvastatin, cyanocobalamin folic acid, esomeprazole, zoledronic acid, magnesium and vitamins.

On day 54, adverse events of elevated AST, elevated ALT, elevated LDH, and elevated GGT were reported. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. Eosinophil levels remained within normal limits throughout the study. There were no physical examination changes at the end of treatment. The adverse events of elevated liver enzymes were reported as not resolved at the time of study completion.

Clinical Review

{Insert Reviewer Name}

{Insert Application Type and Number}

{Insert Product Trade and Generic Name}

Study Day	Alanine Amino transferase (ALT) (normal range 1 - 30 U/L)	Aspartate Amino transferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 20.3 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 - 32 U/L)	Lactate Dehydrogenase (LDH) (normal range 97 - 236 U/L)
-14	19	20	62	6	16	195
1	23	24	65	8.7	17	211
27	17	14	63	10.1	17	207

Study Day	Alanine Amino transferase (ALT) (normal range 1 - 30 U/L)	Aspartate Amino transferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 20.3 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 - 32 U/L)	Lactate Dehydrogenase (LDH) (normal range 97 - 236 U/L)
54	49	42	89	5.8	54	242
71	54	47	85	7.5	87	252

Source: Patient Narrative

Reviewer's Comment: The patient's increases from baseline in serum AST and ALT are negligible. There is no increase in bilirubin, GGT or LDH. Alternative explanations for this modest increase include the use of statins and salicylates, especially since the modest increases did not resolve promptly upon stopping mirabegron.

Subject 2210-71167: Myocardial Ischemia: The subject is a 72 year old Canadian white male randomized to mirabegron 50 mg on 9 October 2009. The subject received a total of 56 days of study drug. The study treatment was discontinued due to the adverse events of silent ischemia on nuclear medicine test (MIBI persantine) on day 56. Medical history included generalized arthrosis (since 1999), peptic ulcer (2003), arterial hypertension (since 2004), gastro-esophageal reflux (GERD) (since 2005), right inguinal hernia (since 2007), benign prostatic hypertrophy (since 2007-05), mouth dryness (since 2009-02), and mild chronic renal insufficiency (since 2009-04). Concomitant medications include acetylsalicylic acid, valsartan, hydrochlorothiazide, and esomeprazole.

On day 54, an adverse event of silent ischemia on nuclear medicine test (MIBI persantine) was reported per the subject's medical internist during a routine cardiac work-up. The subject was treated with oral atorvastatin for a total daily dose of 10 mg and oral metoprolol for a total daily dose of 25 mg for the adverse event. Treatment with the study drug was discontinued on day 56 due to this event. On day 56, the subject experienced an adverse event of bradycardia. The ECG results were abnormal and showed first degree AV block with a heart rate of 57 bpm. No changes were noted in concomitant medications due to this event. The subject had a relevant history of arterial hypertension. These events were considered unresolved at the time of the last study visit.

ECG Findings

Clinical Review

{Insert Reviewer Name}

{Insert Application Type and Number}

{Insert Product Trade and Generic Name}

Study Day	HR Mean (bpm)	PR Mean (ms)	QRS Duration (ms)	RR Mean (ms)	QTCF Mean (ms)	QTCB Mean (ms)	QT Mean (ms)	ECG Interpretation	Comments
-18	59	191	90	1021	395	393	397	normal	-
56	57	211	89	1061	388	384	396	abnormal	first degree AV block

Vital Signs Average

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	150/77	57
Baseline: Office Device	135/79	58
Week 4: Home Device	152/77	58
Week 4: Office Device	150/85	57
Week 8 / Final Visit: Home Device	155/73	50

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Week 8 / Final Visit: Office Device	134/71	49
Follow-Up Visit: Home Device	160/79	45
Follow-Up Visit: Office Device	145/76	44

The patient was also found to have a benign right renal cyst on Study Day 19.

Reviewer's Comment: The circumstances surrounding this event are unclear. A nuclear scan is not a test used for routine cardiac followup. It is possible that the patient had a pre-existing cardiac abnormality that was being followed. Sponsor was contacted and in a 9 December 2011 response to information stated that the MIBI Persantine scan was ordered as part of "a routine cardiac follow-up", although no previous cardiac history was noted in the narrative. The patient also developed bradycardia and findings of first degree AV block on ECG while on study treatment. The relationship between study treatment and the events in this case is unclear.

Reviewer's Overall Comments: There appear to be several cases of tachycardia, and palpitations that may have a relationship to mirabegron. Cardiovascular events reported in clinical studies in the NDA will be reviewed in aggregate under cardiac events of interest as part of the integrated review of safety. Several reports of increased liver enzymes are also noted and these will be reviewed as hepatic events of interest.

Clinical Laboratory

Hematology

No trends in the change from baseline were observed between the mirabegron and placebo groups in hematology variables. When shifts from baseline to the most extreme value were considered, shifts in leukocyte count from normal at baseline to below the LLN occurred in 10 (2.5%) patients in the placebo group, 14 (3.5%) patients in the mirabegron 25 mg group and 14 (3.4%) patients in the mirabegron 50 mg group. Of the 28 mirabegron patients, six had a low

leukocyte at baseline. The lowest leukocyte count during treatment for the 28 mirabegron patient was $2.7 \times 10^9/L$. At study endpoint, 7 of the 28 mirabegron patients, had a leukocyte count below $3.6 \times 10^9/L$. Three of the 28 patients reported a total of 4 TEAEs which were: upper respiratory infection, pyrexia, nasopharyngitis and hematocrit/hemoglobin decreased unresolved at Day 62 (2050-70400). Subject 2050-70400 had baseline erythrocyte, hemoglobin, and hematocrit below normal with small decreases noted during the study.

Two placebo subjects had low platelet counts but started the study with decreased platelets (1630-7173 and 2197-7095). Two mirabegron 25 mg patients had decreased platelet counts ($<120 \times 10^6/L$). One had an isolated count on Day 90 of $112 \times 10^6/L$ having started with a baseline value of $192 \times 10^9/L$. The second (3136-71808) had platelet counts below the LLN at screening, baseline, and on Days 57 and 82. The platelet was below the potentially clinically significant value on Day 82 ($119 \times 10^6/L$). There was one mirabegron 50 mg subject with a decreased platelet count at Day 90 ($111 \times 10^6/L$). At Screening, Day -1, Day 34 and Day 64, this subject's platelet counts were 99, 107, 104 and $97 \times 10^6/L$ respectively.

Reviewer's Comment: There are no obvious mirabegron-related changes in hematology parameters in this study.

Clinical Chemistry

Mean changes from baseline to each visit in serum chemistry variables were generally similar across the treatment groups. Mean increases from baseline to final visit in ALP were slightly greater in the mirabegron 25 mg and 50 mg groups (0.9 U/L and 1.5 U/L) compared to placebo (0.5 U/L). For the parameter of creatinine, a mean increase of 2.8 mcmmol/L was observed in the mirabegron 25 mg treatment group; this value was largely attributed to Patient No. 2053-71945 who had a 574 mcmmol/L increase from baseline in creatinine (88 mcmmol/L at baseline; 662 mcmmol/L at final visit). Upon investigation, this increase for patient 2053-71945 was on the basis of spurious lab value which upon repeat was not confirmed and was within normal limits.

For GGT levels, the incidence of shifts from normal at baseline to high at final visit was 1.7% (6/349), 4.0% (14/350) and 5.0% (18/363) for the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Shifts in HbA1c from normal at baseline to above the ULN occurred in 4.9% (17/346) patients in the placebo group, 7.9% (28/355) patients in the mirabegron 25 mg group and 6.4% (23/360) patients in the mirabegron 50 mg group when extreme values were considered rather than the final visit value. It is also to be noted that more patients taking mirabegron had a decrease in Hgb A1c than patients taking placebo (1.9%, 2.9% and 2.8% for placebo, mirabegron 25 mg and mirabegron 50 mg respectively).

Three patients in the mirabegron 25 mg group had a serum creatinine value that met the PCS criterion. These patients had serum creatinine levels above the ULN at baseline and throughout the study. None of the 3 patients experienced a TEAE related to abnormal renal function. Patient 2053-71945 had normal serum creatinines at screening, baseline and Days 23 and 56. At end of study visit the creatinine was 662 mcmmol/L. A repeat serum creatinine in the emergency room was within normal limits. The incidence of patients whose BUN value met the PCS criterion was

0.5% (2/417), 0.7% (3/418) and 0.2% (1/428) in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. The majority of the patients with a BUN value that met the PCS criterion had a history of diabetes, hypertension or cardiac disorders. With the exception of Patient No. 3011-72018 in the mirabegron 25 mg group, all of these patients had BUN values above the ULN at baseline and throughout the study. Patient No. 3011-72018 had a single value for BUN that was above the ULN which met the PCS criteria; this value occurred after the withdrawal of study drug. No patient had study drug withdrawn due to increased BUN or creatinine.

No patients met laboratory criteria for Hy's Law (i.e., concomitant elevations in ALT and/or AST > 3 times the ULN and total bilirubin > 2 times the ULN). Elevations meeting the PCS criteria for ALT and GGT (3X normal) were observed in patients in all treatment groups. Elevations meeting the PCS criterion for AST were observed in patients in the placebo and mirabegron 25 mg groups (1 patient each) and no patients in the mirabegron 50 mg group. Only 1 patient in the mirabegron 25 mg group had elevated levels of ALP that met the PCS criteria. Two patients in the placebo group, no patients in the mirabegron 25 mg group and 1 patient in the mirabegron 50 mg group had elevated levels of total bilirubin that met the PCS criterion.

Of the patients with hepatic events based on MedDRA query or with PCS hepatic laboratory values, 18 patients were in the mirabegron 25 mg dose group. Of these 6 had transient elevations which resolved by end of study with the exception of one subject who had transient ALT and AST increases (resolving at end of study) but the rise in GGT continued to end of study (baseline GGT 47 U/L [elevated], GGT Day 34 150 U/L, GGT Day 90 52 U/L). 9 subjects had increases of liver enzymes at screening. 2 subjects had history of hepatitis C and one of these two subjects had a history of hepatitis A and B as well. There were no TEAEs reported with these abnormalities.

Of the patients with hepatic events based on MedDRA query or with PCS hepatic laboratory values, 10 patients were in the mirabegron 50 mg dose group. One patient had elevated AST, ALT, bilirubin and GGT at screening, one patient elevated GGT at screening, and one patient had elevated ALP and GGT at screening and at end of study had increased ALT, AST, ALP and GGT. Two patients had hepatic enzyme increases that were transient and resolved by end of study. There was one patient who had normal liver enzymes at baseline and at endpoint had an AST of 62 U/L and an ALT of 143 U/L. One patient had bilirubin elevations at baseline that resolved by study endpoint. One patient had a history of ongoing fatty liver while a second patient had a history of ongoing liver disorder.

No trends in the mean change from baseline to each visit in urine pH were observed between the mirabegron and placebo groups. The incidence of shifts from negative to positive in urine glucose at final visit was 0.3% (1/400), 2.7% (11/409) and 1.4% (6/414) for the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. The incidence of shifts from negative to positive in urine erythrocytes at final visit was 3.7% (14/379), 6.4% (24/374) and 8.3% (32/385) for the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Shifts in nitrites from negative at baseline to positive at final visit occurred in 0.7% (3/411), 1.2% (5/410) and 2.1% (9/422) of patients in the placebo, mirabegron 25 mg and mirabegron 50

mg groups, respectively. The Sponsor observes that the shift in urine erythrocytes is concordant with the shift in nitrites levels in the urine and the increased incidence of UTIs observed in the mirabegron treatment groups. The incidence of other urinalysis parameters was similar across all treatment groups. Of the patients who had positive urine nitrites, a majority of them also had a positive culture and corresponding TEAE of UTI.

Two patients were identified as having high TSH values. One patient had a medical history of hyperthyroidism but without treatment at study start. A second patient had a history of hyperthyroidism and was receiving medical therapy at the start of the study. The TSH level was 0.24 mU/L (low) at baseline and 53.53(elevated) at week 12/final visit.

Reviewer's Comments: There appear to be no discernible trends or safety concerns relative to hematology and clinical laboratory findings in this study.

Vital Signs

Pulse

In the overall population, for AM measurements, a small increase in mean pulse rate (0.8-0.9 bpm) from Baseline to final visit was observed with mirabegron treatment compared to placebo that was not dose-dependent. For the PM measurement, an increase in mean pulse rate was observed with mirabegron treatment compared to placebo (0.6 bpm for mirabegron 25 mg group; 1.1 bpm for mirabegron 50 mg group). This increase appeared to be dose dependent for the PM measurement only. Mean increases in pulse rate with mirabegron relative to placebo were not observed approximately 2 weeks after patients discontinued study drug. A more distinct dose-dependent increase was noted in female patients compared to male patients. Female patients treated with mirabegron 25 mg and mirabegron 50 mg experienced a change from baseline to final visit relative to placebo of 0.5 and 0.9 bpm, respectively for AM measurements and 0.4 and 1.0 bpm, respectively for PM measurements. Changes in pulse rate in patients \geq 65 years of age and patients $<$ 65 years of age were similar to the overall population. There was no subgroup prone to greater increases in pulse rate with mirabegron treatment compared to placebo treatment. These results were consistent with a slightly greater incidence of TEAEs of tachycardia (using broad search terms) in mirabegron-treated patients compared to placebo-treated patients (2.1% versus 0.9%, respectively).

Table 33: Tachycardia Based on Treatment-Emergent Adverse Events and Vital Signs

Type of Event, n(%)	Placebo	Mirabegron 25mg	Mirabegron 50mg
	n=433	n=432	n=440
Any Tachycardia	11 (2.5)	21 (4.9)	15 (3.4)
TEAE of tachycardia	4 (0.9)	10 (2.3)	8 (1.8)
Tachycardia based on vital signs, any visit, AM or PM	7 (1.6)	15 (3.5)	11 (2.5)

Tachycardia at more than 1 time point during the study	2 (0.5)	6 (1.4)	3 (0.7) [includes patient with fibrillation]
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Tachycardia is defined as >100 bpm

Source: Table 45, Study 178-CL-074 Study Report, page 163

Of the 21 mirabegron 25 mg subjects with “any tachycardia”, 10 had tachycardia at either baseline or during the screening period and 5 of the remaining 11 subjects had tachycardia only at a single timepoint during the study. Of the 15 mirabegron 50 mg subjects with “any tachycardia”, one had atrial fibrillation. 10 of these subjects had tachycardia at either baseline or during the screening period. Two mirabegron 50 mg patients had tachycardia at a single time point during the study. Of the 11 placebo subjects with “any tachycardia”, 5 had tachycardia at baseline or during the screening period. There were 4 patients who had tachycardia at only 1 timepoint during the study.

Reviewer’s Comment: The incidence of new tachycardia for the 50 mg mirabegron dose is barely more than the incidence in placebo subjects.

There was only one subject (3132-71646) in the mirabegron 25 mg group who had met the PCS criteria of change to baseline of ≥ 15 bpm or pulse rate ≥ 120 bpm. This patient has diabetes, hypertension, and a history of multifocal cerebral infarction. The patient is taking anafranil which has a side effect of sinus tachycardia.

The normotensive group generally had a higher incidence of patients whose pulse rate measurements met selected criteria whereas hypertensive patients generally had a lower incidence of patients who met these criteria. One possible explanation for this finding is that concurrent use of antihypertensive agents with negative chronotropic effects may have mitigated the magnitude of effect of mirabegron on pulse rate in the hypertensive population.

Blood Pressure

Changes in mean AM and PM SBP and DBP measurements from Baseline to final visit were comparable between the mirabegron 25 mg and placebo groups. For the mirabegron 50 mg group, increases in SBP relative to placebo was 1.5 mm Hg for both the AM and PM measures; for DBP the mirabegron 50 mg group had an increase of 1.0 and 0.5 mm Hg for AM and PM measurements, respectively. The increase from baseline in SBP in the mirabegron 50 mg treatment group for both AM and PM measurements were 0.1 mm Hg compared to placebo group at the follow-up visit after patients had discontinued study drug for approximately 2 weeks. For DBP the AM and PM measurements returned to baseline in the mirabegron 50 mg group at the follow-up visit. Sensitivity analyses on systolic and diastolic blood pressure data that excluded patients who took other OAB medications prior to or during the follow-up visit assessment were performed and the results were consistent with the overall population. Trends similar to the overall population were observed in the normotensive and hypertensive subpopulations. In the 50 mg treatment group, increases in blood pressure at final visit, relative to placebo, were lower in the hypertensive subgroup compared to the normotensive

and overall populations.

Table 34: Change From Baseline to Final Visit in AM and PM Blood Pressure by Patient Diary Study 178-CL-074

Population	Placebo		Mirabegron			
			25 mg		50 mg	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
Overall Population	(n=433)		(n=432)		(n=440)	
n	415	415	410	410	427	427
Baseline mean (SE)	128.3 (0.82)	76.5 (0.45)	129.2 (0.81)	78.2 (0.48)	131.1 (0.85)	77.4 (0.46)
Mean difference vs placebo (SE) AM			-0.1(0.64)	0.2 (0.39)	1.5 (0.64)	1.0 (0.38)
Mean difference PM			-0.6(0.46)	-0.1(0.29)	1.5 (0.64)	0.6(0.28)
Normotensive Pop	(n=267)		(n=250)		(n=268)	
n	257	257	239	239	263	263
Baseline mean (SE)	124.2 (0.98)	75.9 (0.55)	123.8 (0.97)	76.4 (0.58)	126.8 (1.02)	77.0 (0.58)
Mean difference vs placebo (SE) AM			0.1 (0.74)	0.2 (0.50)	1.9 (0.72)	1.1 (0.49)
Mean difference PM			-0.5(0.65)	-0.2(0.41)	1.5 (0.64)	0.5 (0.40)
Hypertensive Pop	(n=166)		(n=182)		(n=172)	
n	158	158	171	171	164	164
Baseline mean (SE)	135.1 (1.29)	77.5 (0.77)	136.8 (1.16)	80.8 (0.76)	137.9 (1.34)	78.0 (0.75)
Mean difference vs placebo (SE) AM			-0.6(1.16)	0.1 (0.62)	0.8 (1.18)	0.8 (0.62)
Mean difference PM			-1.0(1.13)	-0.4(0.64)	1.0(1.14)	0 (0.64)

Source: Table 74 and 75, Study Report 178-CL-074, pages 213 and 214. The “PM mean differences” in blood pressure were added from study report table 75 for comparison of AM and PM blood pressure changes. The n numbers are from study report Table 74 (AM).

Reviewer’s Comments: In this study, the overall elevations of the blood pressure were greater for the 50 mg mirabegron dose than for the 25 mg mirabegron dose. The 25 mg dose was comparable to placebo in its effect on blood pressure. Also in this study, the AM blood pressures were determined immediately upon arising and without eating. The PM blood pressure measurements were performed between 2 and 6 PM. Study drug dose administration is scheduled in the morning. It is possible that neither the AM or PM blood pressure measurements captured blood pressure at peak mirabegron exposure.

In Phase 1 studies, such as Study 178-CL-080, a larger single dose of mirabegron (100 mg) was associated with a small increase in change from baseline SBP, both as a single dose and in combination with tamsulosin. Small changes from baseline in diastolic BP were also observed. This study was performed in healthy volunteers. The peak effect of mirabegron 100 mg on the supine systolic blood pressure in Study 080 was 2.48 mmHg and 3.32 mm Hg at 2 and 4 hours, respectively.

The reasons for the difference in mirabegron-related increases in blood pressure in Phase 3 and Phase 1 studies remains unclear.

The following tables are analyses of BP outliers for AM and PM systolic and diastolic BP.

Table 35: Blood Pressure Outliers AM/PM Systolic Blood Pressure Study 178-CL-074

Parameter, n/n (%)		Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Overall		n=433	n=432	n=440
Final Visit	AM /PM Systolic			
Change from Baseline ≥ 15 mmHg AM		16/415 (3.9%)	21/410 (5.1%)	29/427 (6.8%)
Change from Baseline ≥ 15 mmHg PM		25/414 (6.0%)	23/410 (5.6%)	32/427 (7.5%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg AM		25/378 (6.6%)	25/378 (6.6%)	30/399 (7.5%)
Change from Baseline ≥ 10 mmHg PM		33/378 (8.7%)	26/396 (6.6%)	26/396 (6.6%)
Change from Baseline ≥ 15 mmHg AM		9/378 (2.4%)	6/396 (1.5%)	6/399 (1.5%)
Change from Baseline ≥ 15 mmHg PM		12/378 (3.2%)	8/396 (2.0%)	8/396 (2.0%)
Change from Baseline ≥ 20 mmHg AM		3/378 (0.8%)	2/396 (0.5%)	5/399 (1.3%)
Change from Baseline ≥ 20 mmHg PM		6/378 (1.6%)	4/396 (1.0%)	4/396 (1.0%)
Normotensive		n=267	n=250	n=268
Final Visit	AM/PM Systolic			
Change from Baseline ≥ 15 mmHg AM		5/257 (1.9%)	10/239 (4.2%)	16/263 (6.1%)
Change from Baseline ≥ 15 mmHg PM		7/256 (2.7%)	11/239 (4.6%)	18/263 (6.8%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg AM		9/237 (3.8%)	15/231 (6.5%)	20/244 (8.2)
Change from Baseline ≥ 10 mmHg PM		15/237 (6.3%)	17/231 (7.4%)	20/244 (8.2)
Change from Baseline ≥ 15 mmHg AM		1/237 (0.4%)	1/231 (0.4%)	5/244 (2.0%)
Change from Baseline ≥ 15 mmHg PM		1/237 (0.4%)	5/231 (2.2%)	6/244 (2.5)
Change from Baseline ≥ 20 mmHg AM		0	1/231 (0.4%)	4/244 (1.6%)
Change from Baseline ≥ 20 mmHg PM		1/237 (0.4%)	2/231 (0.9%)	2/244 (0.8%)
Hypertensive		n=166	n=182	n=172
Final Visit	AM/PM Systolic			
Change from Baseline ≥ 15 mmHg AM		11/158 (7.0%)	11/171 (6.4%)	13/164 (7.9%)
Change from Baseline ≥ 15 mmHg PM		18/158 (11.4%)	12/171 (7.0%)	14/164 (8.5%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 10 mmHg AM		16/141 (11.3%)	19/165 (11.5%)	10/155 (6.5%)
Change from Baseline ≥ 10 mmHg PM		18/141 (12.8%)	9/165 (5.5%)	15/155 (9.7%)
Change from Baseline ≥ 15 mmHg AM		8/141 (5.7%)	5/165 (3.0%)	1/155 (0.6%)
Change from Baseline ≥ 15 mmHg PM		11/141 (7.8%)	3/165 (1.8%)	7/155 (4.5%)

Change from Baseline ≥ 20 mmHg AM	3/141 (2.1%)	1/165 (0.6%)	1/155 (0.6%)
Change from Baseline ≥ 20 mmHg PM	5/141 (3.5%)	2/165 (1.2%)	3/155 (1.9%)

Source: Table 77 and 79, Study Report 178-CL-074, pages 219 and 221.

Reviewer's Comment: There are few differences between 25 mg and placebo in any category of systolic BP outlier. In normotensive subjects, the percent of systolic PM outliers is increased as compared to placebo in the change from baseline to endpoint of ≥ 15 mmHg and modestly increased in all 2 consecutive baseline categories.

Table 36: Diastolic AM/PM Blood Pressure Outliers Study 170-CL-074

Parameter, n/n (%)		Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Overall		n=433	n=432	n=440
Final Visit	AM /PM Diastolic			
Change from Baseline ≥ 10 mmHg AM		13/415 (3.1%)	17/410 (4.1%)	27/427 (6.3%)
Change from Baseline ≥ 10 mmHg PM		17/414 (4.1%)	18/410 (4.4%)	25/427 (5.9%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg AM		35/378 (9.3%)	47/396 (11.9%)	58/399 (14.5%)
Change from Baseline ≥ 5 mmHg PM		55/378 (14.6%)	43/396 (10.9%)	63/399 (15.8%)
Change from Baseline ≥ 10 mmHg AM		5/378 (1.3%)	5/396 (1.3%)	11/399 (2.8%)
Change from Baseline ≥ 10 mmHg PM		7/378 (1.9%)	9/396 (2.3%)	13/399 (3.3%)
Change from Baseline ≥ 15 mmHg AM		0	1/396 (0.3%)	2/399 (0.5%)
Change from Baseline ≥ 15 mmHg PM		0	1/396 (0.3%)	1/399 (0.3%)
Normotensive		n=267	n=250	n=268
Final Visit	AM/PM Diastolic			
Change from Baseline ≥ 10 mmHg AM		8/257 (3.1%)	10/239 (4.2%)	18/263 (6.8%)
Change from Baseline ≥ 10 mmHg PM		9/256 (3.5%)	10/239 (4.2%)	18/263 (6.8%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg AM		21/237 (8.9%)	31/231 (13.4%)	39/244 (16.0%)
Change from Baseline ≥ 5 mmHg PM		32/237 (13.5%)	28/231 (12.1%)	44/244 (18.0%)
Change from Baseline ≥ 10 mmHg AM		2/237 (0.8%)	3/231 (1.3%)	8/244 (3.3%)

Change from Baseline ≥ 10 mmHg PM	3/237 (1.3%)	6/231 (2.6%)	10/244 (4.1%)
Change from Baseline ≥ 15 mmHg AM	0	0	2/244 (0.8%)
Change from Baseline ≥ 15 mmHg PM	0	0	1/244 (0.4%)
Hypertensive	n=166	n=182	n=172
Final Visit	AM/PM		
	Diastolic		
Change from Baseline ≥ 10 mmHg AM	5/158 (3.2%)	7/171 (4.1%)	9/164 (5.5%)
Change from Baseline ≥ 10 mmHg PM	8/158 (5.1%)	8/171 (4.7%)	7/164 (4.3%)
2 Consecutive Postbaseline Visits			
Change from Baseline ≥ 5 mmHg AM	14/141 (9.9%)	16/165 (9.7%)	19/155 (12.3%)
Change from Baseline ≥ 5 mmHg PM	23/141 (16.3%)	15/165 (9.1%)	19/155 (12.3%)
Change from Baseline ≥ 10 mmHg AM	14/141 (9.9%)	2/165 (1.2%)	3/155 (1.9%)
Change from Baseline ≥ 10 mmHg PM	4/141 (2.8%)	3/165 (1.8%)	3/155 (1.9%)
Change from Baseline ≥ 15 mmHg AM	0	1/165 (0.6%)	0
Change from Baseline ≥ 15 mmHg PM	0	1/165 (0.6%)	0

Source: Tables 78 and 80, Study Report 178-CL-074, pages 220 and 222.

Reviewer's Comment: There are few diastolic BP outlier categories where 25 mg exceeds placebo. In the overall and normotensive groups, 50 mg mirabegron patients had more changes from baseline to endpoint of ≥ 5 mmHg and ≥ 10 mmHg in both AM and PM groups as compared to placebo, with the difference more notable in the ≥ 5 mmHg category. The 50 mg overall and normotensive mirabegron groups also had greater numbers of subjects with increased as compared to placebo in the ≥ 5 and ≥ 10 mmHg 2 Consecutive Postbaseline Visits blood pressure categories.

The Sponsor has identified subjects (using patient diaries) with potentially clinically significant changes from baseline to final visit in AM or PM *systolic* blood pressure averages. As a definition of clinical significance, the average blood pressure systolic had to be ≥ 180 mmHg or an increase ≥ 20 mmHg over baseline. One mirabegron 25 mg subject (**3246-7121**) was identified as having an AM average blood pressure of 181.5 mmHg which was a change of 21.8 mmHg from AM average baseline. This patient was hypertensive on medication at baseline. On Day -6, this patient's average blood pressure in the AM was 183 mmHg. This patient's systolic blood pressure ranged from 130-196 mmHg throughout the study. Two mirabegron 50 mg patients were identified with PCS changes. For patient **3089-71108**, the average baseline pressure as determined by office device was 146/77 mmHg. The patient's average baseline PM systolic blood pressure was 172.7 mmHg. On Day -4, the patient's average PM blood pressure was 198 mmHg. The range of systolic blood pressure during the screening period was 139-202

mmHg. On Day 63, the patient was noted to have a TEAE of “hypertension”. Despite the elevated BP’s during the screening period, there was no past medical history of hypertension. The patient’s PM blood systolic pressures on Day 118 were 194, 176, 176 mmHg. The final visit PM systolic blood pressure is reported by Sponsor as 195.0 mmHg. For patient **1607-72065**, the average baseline pressure as determined by office device was 142/68 mmHg. The average baseline AM systolic blood pressure was 157.5 mmHg. On Day -4, the patient’s average AM blood pressure was 171mmHg (the highest screening value). The range of systolic blood pressure in the screening period was 127-167 mmHg. There was no past history of hypertension. The AM blood systolic pressures on Day 118 were 194, 176, 176 mmHg. The final visit AM systolic blood pressure is reported by Sponsor as 195.0 mmHg. The final visit AM systolic average blood pressure was 189 mmHg. The followup home and office blood pressures were 134 and 133 mmHg respectively.

Reviewer’s Comment: For all three patients, the systolic blood pressures were elevated from normal baseline values prior to drug therapy. Of the three patients with PCS increased systolic blood pressure on mirabegron, only 1 (1607-72065) had a clinically meaningful blood pressure increase for which causality with mirabegron could not be excluded, because in this patient, the post-baseline maximum systolic BP was almost 20 mm Hg higher than the maximum pre-baseline systolic BP .

The Sponsor also has identified subjects (using patient diaries) with potentially significant changes from baseline to final visit in AM or PM *diastolic* blood pressure averages. For clinical significance the average diastolic blood pressure systolic had to be ≥ 105 mmHg or increase ≥ 15 mm Hg over baseline. For patient 2031-71925, the average baseline AM diastolic pressure as determined by office device was 89.8 mmHg. On Day -4, the patient’s average AM blood pressure was 97.3 mmHg (the highest screening value). The range of diastolic blood pressure in the screening period was 63-103 mmHg. There was no past history of hypertension. The followup AM average diastolic blood pressure 96 mmHg. For patient 2168-71991, the average baseline AM diastolic pressure as determined by office device was 90.5 mmHg. The patient has a medical history of hypertension and is taking metoprolol and lisinopril. On Day -5, the patient’s average AM blood pressure was 118.6 mmHg (the highest screening value). The range of diastolic blood pressure in the screening period was 93-127 mmHg. The final visit AM systolic blood pressure is reported by Sponsor as 195.0 mmHg. The final visit AM diastolic average blood pressure was 106 mmHg. The followup average AM blood pressure was 98 mmHg.

Reviewer’s Comment: Both of these subjects appear to have pre-existing with very significantly elevated baseline diastolic blood pressures (hypertension). With dechallenge of mirabegron, both patients remained hypertensive.

Mean changes from baseline to final visit in AM and PM SBP for the mirabegron 50 mg treated patients relative to placebo were generally larger in female patients (AM: 1.6 mm Hg; PM: 2.1 mm Hg) than in male patients (AM: 1.4 mm Hg; PM: 0.4 mm Hg). A similar trend was observed for mean changes from baseline to final visit in AM and PM DBP (Females AM: 1.4,

PM: 0.8 mm Hg; Males AM: 0.2, PM -0.2 mm Hg). Mean changes from baseline to final visit in AM and PM SBP for the mirabegron 50 mg treated patients relative to placebo were generally larger in patients < 65 years of age (AM: 2.1 mm Hg; PM: 1.8 mm Hg) than in patients \geq 65 years of age (AM: 0.7 mm Hg; PM: 1.1 mm Hg). A similar trend was observed for mean changes from baseline to final visit in AM and PM DBP (< 65 years AM: 1.4, PM: 0.9 mm Hg; \geq 65 years AM: 0.4, PM -0.0 mm Hg).

The adjusted mean difference from baseline to final visit in SBP versus placebo in mirabegron-treated patients \geq 75 years of age ranged from -2.0 to 2.8 mm Hg while in patients < 75 years of age they ranged from -0.5 to 1.4 mm Hg for AM and PM measurements. The adjusted mean difference from baseline to final visit in DBP versus placebo in mirabegron-treated patients \geq 75 years of age ranged from 0.3 to 2.0 mm Hg while in patients < 75 years of age they ranged from -0.4 to 0.9 mm Hg for AM and PM measurements. The small number of patients in the age group of \geq 75 years of age relative to the overall population which precludes the Sponsor from drawing formal conclusions regarding these changes.

According to the Sponsor, the incidence of treatment-emergent hypertension reported as a clinical AE (based on PT and SMQ) was similar between the mirabegron 25 mg and mirabegron 50 mg groups but was higher for both mirabegron groups than for the placebo group, which is discordant from the actual blood pressure measurements, for which the placebo and mirabegron 25 mg groups are similar.

Reviewer's Comment: By my analysis, which done in a different manner than the Sponsor used, I did not conclude that there was an increased incidence of hypertension as a clinical AE in mirabegron subjects compared to placebo patients.

ECGs

Mean increases from baseline to final visit in ECG-measured heart rate were numerically higher in female patients compared to male patients across all treatment groups. The change from baseline to final visit in females for placebo, mirabegron 25 mg and mirabegron 50 mg were 2.8, 2.7 and 3.8 bpm respectively. The change from baseline to final visit in males for placebo, mirabegron 25 mg and mirabegron 50 mg were 1.2, 2.6 and 2.0 bpm respectively.

No patient had a QTcF > 500 msec. QTcF absolute values > 480 msec were observed for 1 patient (0.2%) in the mirabegron 50 mg group only. The incidence of QTcF absolute values > 450 msec was comparable across all treatment groups. The incidence of a \geq 30 msec increase in QTcF was similar across all treatment groups. Two patients, 1 each in the placebo and mirabegron 25 mg groups, had \geq 60 msec increases in QTcF. Patient No. 3225-70901 in the placebo group had a QTcF interval of 387.0 msec at baseline and 455.0 msec at week 12/final visit, reflecting a 68 msec increase from baseline. Patient No. 3367-71895 in the mirabegron 25 mg group had a QTcF interval of 385.0 msec at baseline and 467.0 msec at week 12/final visit, reflecting an 82 msec increase from baseline.

Ectopic ventricular arrhythmias occurred with highest incidence in the placebo group (3.0%) compared to the mirabegron 25 mg and mirabegron 50 mg treatment groups (1.7% and 1.2%, respectively). The incidence of low grade AV block occurred in 2.5%, 1.0% and 3.4% of patients in the placebo, mirabegron 25 mg and mirabegron 50 mg treatment groups, respectively.

Treatment-emergent sinus tachycardia, defined by the central reader as mean heart rate > 100 bpm and mean PR interval not null, was similar across treatment groups and occurred in 2 (0.5%), 4 (1.0%) and 3 (0.7%) patients in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. Two patients in the mirabegron treatment groups (one each in the 25 mg and 50 mg groups) compared to no patients in the placebo group had treatment-emergent atrial fibrillation. In a separate analysis (Section 9.1.3.1.3.1), the Sponsor identified 1 (0.2%) patient in the placebo group [Patient No. 3225-70844], 1 (0.2%) patient in the mirabegron 25 mg group [Patient No. 2179-70684], and 2 patients (0.5%) in the mirabegron 50 mg group [Patient No. 1534-72081 and Patient No. 1580-70950] as having treatment-emergent atrial fibrillation of medical importance.

Treatment-emergent first degree AV block, defined by the central reader as mean PR interval > 200 msec, occurred in 10 (2.5%), 4 (1.0%), and 14 (3.4%) of patients in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively.

Postvoid Residual Urine

The mean change from baseline to final visit in PVR volume was comparable across all treatment groups [Table 91]. One patient, a 46-year-old female, in the mirabegron 25 mg treatment group (Patient No. 2064-70158) had a PVR volume of 566 mL at baseline. PVR volume for this patient was 121 mL at week 12/final visit. No other patients in any treatment group had a PVR volume > 500 mL during the study. The change from baseline to final visit for PVR for placebo, mirabegron 25 mg and mirabegron 50 mg was -2.1 mL, -3.0 mL and 1.0 mL respectively. Shifts to PVR > 300mL occurred in 2 placebo patients and 1 patient each in the mirabegron 25 and 50 mg groups. Overall male patients experienced larger magnitude increases in PVR.

Overall Conclusions

In this study, mirabegron at doses of 25 and 50 mg once daily for 12 weeks demonstrated efficacy based on the co-primary endpoints of incontinence episodes and micturition frequency per 24 hours. The mirabegron 50 mg dose met more of the secondary efficacy outcomes than the mirabegron 25 mg dose demonstrating that both doses are effective but that 25 mg is not a maximally effective dose. Mirabegron 50 mg, but not mirabegron 25 mg, was effective at the first measured time post-dose at week 4 as assessed by a reduction in incontinence episodes per 24 hours. At Week 8, both doses achieved statistically significant and comparable improvements from baseline in both primary endpoints. The statistically significant reduction in incontinence episodes noted with treatment with both mirabegron 25 mg and 50 mg (adjusted mean difference versus placebo of -0.40 and -0.42, respectively) represents a clinically meaningful improvement.

The eligibility criterion did not require a minimum number of incontinence episodes at baseline. This could have constrained the magnitude of the drug effect.

Mirabegron 25 mg did not demonstrate statistically significant improvement in mean volume voided per micturition which precluded further statistical testing for this dose for the remaining secondary endpoints. Furthermore, because of the multiplicity adjustment once mirabegron 25 mg failed to reach statistical significance, further testing on the mirabegron 50 mg dose was performed at a significance level of 0.025. Despite the more stringent threshold for statistical significance, mirabegron 50 mg demonstrated efficacy for the key secondary variables of change from baseline to final visit relative to placebo in mean volume voided per micturition and change from baseline to final visit relative to placebo in incontinence episodes per 24 hours at week 4 (the first post-dose measurement).

A detailed definition for hypertension was prespecified in the protocol similarly to prior Phase 3 efficacy studies. The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was higher in mirabegron-treated patients than in the placebo treatment group (8.5%, 12.0 % and 11.1% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively). This finding was not observed in the previous phase 3 studies, which evaluated doses of 50 and 100 mg mirabegron [see Studies 178-CL-046 and 178-CL-047].

Reviewer's Comment: By my analysis, using a different method than the Sponsor utilized, there does not appear to be an increased incidence of hypertension in this study. This is largely due to the occurrence of hypertension at baseline in many of these cases, without significant worsening while on treatment.

There were few SAEs and few discontinuations due to AEs in this study. The mirabegron-related common AEs were also infrequent and included nasopharyngitis, UTI, as in previous studies, and in this study, dizziness. Patients treated with mirabegron 50 mg experienced small increases relative to placebo in SBP for both AM (1.5 mm Hg) and PM (1.5 mm Hg) measurements. In an outlier analysis, there was an increased incidence of outliers for mirabegron 50 mg compared to placebo with mostly mild BP outlier increases (e.g., ≥ 5 or ≥ 10 mm Hg systolic BP). Patients treated with mirabegron 50 mg also experienced small increases in AM DBP (1.0 mm Hg) measurements relative to placebo-treated patients. Normotensive patients, female patients and patients < 65 years of age experienced larger increases in blood pressure measurements relative to placebo than hypertensive patients, male patients and those ≥ 65 years of age, respectively. Increases in blood pressure with 25 mg appeared comparable to increases with placebo.

Tachycardia as a clinical AE (PT) was reported at a higher rate in the mirabegron treatment groups (1.6% each) compared to placebo (0.9%). Comparable results were observed using a broader search of preferred terms. The incidence of tachycardia when TEAEs and vital signs were assessed concurrently was also slightly higher with mirabegron treatment compared to placebo; no trend by dose was observed. Small increases from baseline to final visit in mean pulse rate were observed with mirabegron treatment compared to placebo (0.8 and 0.9 bpm for

AM measurements and 0.6 and 1.1 bpm for PM measurements in the mirabegron 25 mg and mirabegron 50 mg groups, respectively).

No consistent trends in ECG changes were identified. There was no evidence of increased incidence of QTc interval prolongation or its sequelae in mirabegron-treated patients.

There were no reports of syncope in this study. There were no reported seizures in mirabegron-treated patients; grand mal convulsion and petit mal epilepsy each occurred in 1 patient in the placebo group.

Urinary retention (including acute urinary retention) was not observed in mirabegron-treated patients compared to 1 patient in the placebo group. No patients experienced extreme events in PVR volume that required intervention.

The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders SMQ, was similar across treatment groups. Most hepatic TEAEs were mild or moderate in intensity and were rarely treatment limiting.

Study 178-CL-049: A Randomized, Double-Blind, Double-Dummy, Parallel Group, Active Controlled, Multi-center Long-term Study to Assess the Safety and Efficacy of the Beta-3 Agonist Mirabegron (YM178) 50 mg qd and 100 mg qd in Subjects With Symptoms of Overactive Bladder

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

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

Study Design: After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline (visit 2), patients who met inclusion criteria and did not meet exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg or tolterodine ER 4 mg once daily for 12 months. Patients with previous or current malignant disease of the pelvic organs were excluded. The randomized, double-blind, double-dummy, active-controlled treatment period consisted of visits at months 1, 3, 6, 9 and 12. Patients who completed the 12-week treatment and safety follow-up periods of studies 178-CL-046 or 178-CL-047 in any treatment group (placebo,

mirabegron or tolterodine ER 4 mg) could enroll in 178-CL-049 after being off study medication for at least 30 days, as well as patients that did not participate in the 178-CL-046 or 178-CL-047 studies (naive patients) could be enrolled into this study, if they met all inclusion criteria and none of the exclusion criteria at visit 1 and visit 2.

2849 patients enrolled and 2452 patients were randomized as follows:

- Full analysis set: 2382 patients: mirabegron 50 mg: 789 patients; mirabegron 100 mg: 802 patients; tolterodine ER 4 mg 791 patients
- Full analysis set - Incontinence (representing subjects with incontinence at baseline): 1450: mirabegron 50 mg: 479 patients; mirabegron 100 mg: 483 patients; tolterodine ER 4 mg 488 patients
- Safety analysis set: 2444 patients: mirabegron 50 mg: 812 patients; mirabegron 100 mg: 820 patients; tolterodine ER 4 mg 812 patients

The inclusion/exclusion criteria were the same as for the primary studies and criteria were added to accommodate precautions for the use of tolterodine. Subjects who completed Studies 178-CL-046 or 178-CL-047, or subjects who were treatment naïve were allowed to enroll.

The study had a single-blind run-in period of 2 weeks. The double-blind, active-controlled treatment period was 12 months.

The efficacy variables in this study were secondary objectives and included:

- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of micturitions per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of incontinence episodes per 24 hours (in subjects with incontinence at baseline)
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean volume voided per micturition
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency episodes (grade 3 and/or 4 [grade 4 reflects an urge incontinence episode]) per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean level of urgency
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in the mean number of pads used per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of nocturia episodes per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in Symptom Bother and health related quality of life scores as assessed by the OAB questionnaire (OAB-q)
- Change from baseline to months 3, 6, 12 and Final Visit in scores as assessed by Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP)
- Change from baseline to month 1, 3, 6, 9, 12 and Final Visit in scores as assessed by European Quality of Life-5 Dimensions (EQ-5D) questionnaire

- Change from baseline to months 12 and Final Visit in Patient Perception of Bladder Condition (PPBC)
- Change from baseline to months 12 and Final Visit in the Treatment Satisfaction Visual Analog Scale (TS-VAS)
- Change from baseline to months 3, 6, 12 and Final Visit in the number of physician visits for the patient's bladder condition (excluding study related visits)

Efficacy responder analyses included:

- “Zero incontinence episodes”: a responder was defined as a patient with 0 incontinence episodes Postbaseline.
- “Reduction in incontinence episodes”: a responder was defined as a patient with a $\geq 50\%$ decrease from baseline in mean number of incontinence episodes per 24 hours.

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

Secondary safety variables included:

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

Statistical Methods:

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

All efficacy analyses were based on the FAS with the exception of incontinence episodes and urgency incontinence episodes, for which the FAS-I was used. For the efficacy variables derived from the micturition diary, both the actual values as well as the changes from baseline were summarized descriptively by treatment and visit (including Final Visit) using mean, SE, median, minimum, and maximum. Two models were used to analyze efficacy variables: a repeated measures model and an analysis of covariance (ANCOVA) model. Factors in the repeated measures model included previous study history, sex, geographical region, randomized treatment group, time, randomized treatment by time interaction and sex by time interaction. Co-variates in the model included baseline and baseline by time interaction. Factors in the ANCOVA model included previous study history, sex, geographical region and randomized treatment group. Baseline was the only covariate in the ANCOVA model. Both models were used to obtain adjusted mean changes from baseline along with 95% confidence intervals.

Efficacy Results: Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturitions per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours in subjects with baseline incontinence (adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables. Numerically similar results and a similar course of improvement over time were observed with tolterodine ER 4 mg.

Table 37: Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Mirabegron		Tolterodine
	50 mg (n=479)	100 mg (n=483)	SR 4 mg (n=488)
Baseline			
Mean (SE)	2.66 (0.120)	2.49 (0.113)	2.42 (0.107)
Final Visit			
Mean (SE)	1.61 (0.130)	1.26 ((0.104)	1.19 (0.094)
Change from Baseline			
Mean (SE)	-1.05 (0.102)	-1.24 (0.105)	-1.23 (0.086)

Source: Table 13, Study 178-CL-049 Report, page 96

Table 38: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Mirabegron		Tolterodine
	50 mg (n=789)	100 mg (n=802)	SR 4 mg (n=791)
Baseline			
Mean (SE)	11.13 (0.100)	116 (0.102)	10.94 (0.093)
Final Visit			
Mean (SE)	9.85 (0.110)	9.73 (0.113)	9.58 (0.109)
Change from Baseline			
Mean (SE)	-1.28 (0.087)	-1.43 (0.085)	-1.36 (0.087)

Source: Table 14, Study 178-CL-049 Report, page 99

The Sponsor states that Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturitions per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours

(adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables.

Reviewer's Efficacy Conclusion: In Study 049, it appears that efficacy was maintained through 12 months of mirabegron therapy. Efficacy results between mirabegron (50 mg and 100 mg) and tolterodine SR 4 mg appeared comparable.

Safety:

Study 178-CL-049: This was a 52 week long term safety study with an active comparator arm. Patients were randomized to 3 treatment arms on a 1:1:1 basis. The treatment arms were mirabegron 50 and 100 mg once a day, and tolterodine extended release (ER) 4 mg once a day.

The Sponsor's Safety conclusions were:

- The overall incidence of patients with TEAEs was comparable across treatment groups with reported incidence of 59.7% in the mirabegron 50 mg group, 61.3% in the mirabegron 100 mg group and 62.6% in the tolterodine ER 4 mg group.
- A time to event evaluation on the most common TEAEs demonstrated:
 - The time to first occurrence of hypertension reported as an AE (based on PT) was consistent across the treatment groups and manifested within the first 3 months of treatment, however, onset of events were observed throughout the 1 year duration of the study.
 - The time to first occurrence of dry mouth was reported with a higher incidence in the tolterodine ER 4 mg group relative to the mirabegron treatment groups and manifested within the first month of treatment, however, onset of events were observed throughout the 1 year duration of the study.
 - Time to first onset of UTI, cystitis and tachycardia occurred evenly throughout the duration of the study across all treatment groups.
- Five deaths were reported, of which 4 were considered treatment-emergent:
 - Two treatment-emergent deaths occurred in the mirabegron 50 mg treatment group.
 - One patient had a fatal AE of cardiac failure on day 190 (last dose: day 190) which was not considered to be related to study medication.
 - One patient died on day 108 after experiencing multiple organ failure secondary to sepsis with onsets of adverse events ranging from day 104 to day 107. Pneumonia was the only event considered to be possibly related to study medication. The last dose of study drug was unknown (estimated to be day 86).
 - Two treatment-emergent deaths occurred in the tolterodine ER 4 mg treatment group:

- One patient had a fatal AE of coronary artery disease on day 208 (last dose: day 208) which was not considered to be related to study medication.
- One patient died on day 72 after experiencing fatal AEs of cerebrovascular accident and pneumonia aspiration which began on day 62. The last dose of study medication was on day 62. The events were not considered to be related to study medication.
- A non-treatment-emergent death (completed suicide) occurred in a mirabegron 50 mg-treated patient; the patient died on day 359, 93 days after the last study drug kit (containing 105 days worth of study drug) was dispensed. The actual last dose date for this patient was unknown but was estimated to be day 267 (per imputation rules in the SAP). The investigator considered the completed suicide as possibly related to study drug.
- The overall incidence of patients with treatment-emergent SAEs was 5.2%, 6.2% and 5.4% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.
 - A higher incidence of SAEs in the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) was observed in the mirabegron 100 mg group (1.3%) compared to mirabegron 50 mg (0.1%) or tolterodine ER 4 mg (0.5%). The reported neoplasms were heterogeneous in tissue of origin.
- The overall incidence of patients who discontinued study drug due to a TEAE was 5.9%, 6.1% and 5.7% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.
- For events of interest:
 - The overall incidence of hypertension TEAEs, based on the Hypertension SMQ, was similar across treatment groups: 11.0% in the mirabegron 50 mg group, 10.1% in the mirabegron 100 mg group and 10.6% in the tolterodine ER 4 mg group.
 - TEAEs of QTc prolongation in the Torsades de pointes/QT prolongation SMQ were observed in 8 patients, including 3 patients (0.4%) in the mirabegron 50 mg group, 2 patients (0.2%) in the mirabegron 100 mg group and 3 patients (0.4%) in the tolterodine ER 4 mg group. Of these, 1 patient in the mirabegron 50 mg group experienced SAEs of cardiac arrest, myocardial infarction, ventricular tachycardia and ventricular fibrillation which led to permanent discontinuation of study drug. The cardiovascular adjudication committee adjudicated all of these concurrent cardiovascular events as a nonfatal myocardial infarction in this patient. There was no evidence of Torsades de pointes among the events retrieved by the Torsades de pointes/QT prolongation SMQ.
 - The overall incidence of cardiac arrhythmia TEAEs, based on the Cardiac Arrhythmias SMQ, was 3.9% in the mirabegron 50 mg group, 4.1% in the mirabegron 100 mg group and 6.0% in the tolterodine ER 4 mg group. Cases of atrial fibrillation of medical importance (based on predefined criteria) were noted in 7 (0.9%) patients in the mirabegron 50 mg group, 4 (0.5%) patients in the mirabegron 100 mg group and 9 (1.1%) patients in the tolterodine ER 4 mg group.

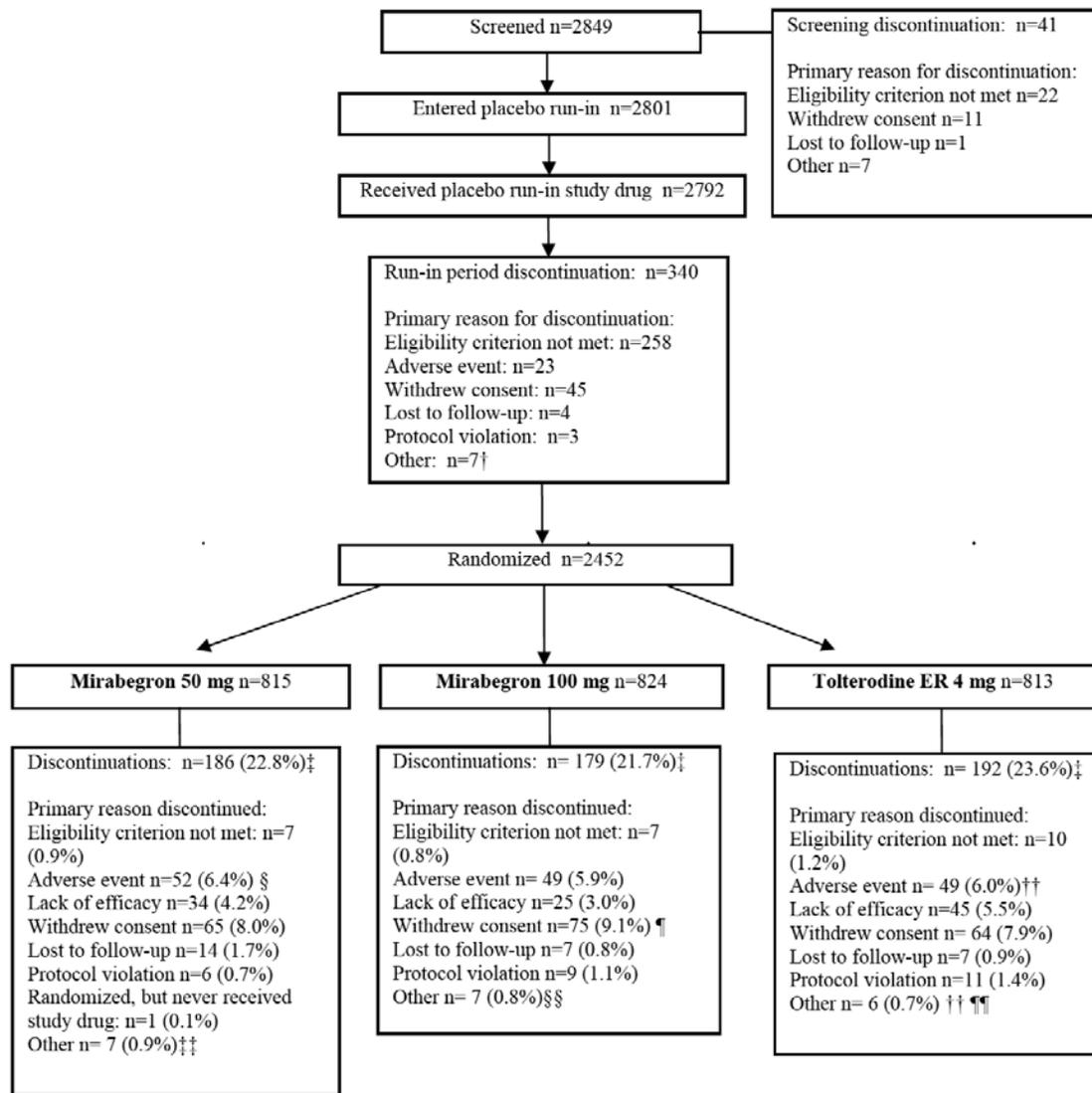
-
- The overall incidence of TEAEs adjudicated as an APTC/MACE cardiovascular event was 0.7% in the mirabegron 50 mg group, 0% in the mirabegron 100 mg group and 0.5% in the tolterodine ER 4 mg group.
 - TEAEs of urinary retention (PT) were reported for 1 patient in the mirabegron 50 mg group, 1 patient in the mirabegron 100 mg group, and 3 patients in the tolterodine ER 4 mg group. Two of these patients reported acute urinary retention requiring catheterization: 1 patient (0.1%) in the mirabegron 100 mg group and 1 patient (0.1%) in the tolterodine ER 4 mg group.
 - The overall incidence of TEAEs indicative of potential hypersensitivity (identified through a comprehensive MedDRA search of PTs indicative of hypersensitivity) was 5.5% in the mirabegron 50 mg group, 5.4% in the mirabegron 100 mg group and 5.2% in the tolterodine ER 4 mg group. Medical evaluation identified 14 patients with events of “likely hypersensitivity.” These patients experienced (1) symptoms and course consistent with drug hypersensitivity reaction, although drugs other than mirabegron could have been implicated, and (2) no explanation other than drug hypersensitivity was documented. Seven patients were considered to have had a hypersensitivity reaction attributable to a source other than study drug, such as concomitant medication. The remaining patients with “likely hypersensitivity” where study drug may have been a precipitating factor, include 3 patients in the mirabegron 50 mg group, 3 patients in the mirabegron 100 mg group and 1 patient in the tolterodine ER 4 mg group
 - Syncope was observed in 1 (0.1%) patient in the mirabegron 50 mg group and 1 (0.1%) patient in the tolterodine ER 4 mg group. In both subjects there were confounding factors, which may have caused the syncope.
 - No episodes of seizure were observed during the study.
 - Hepatic events:
 - The overall incidence of hepatic TEAEs, based on the Possible Drug-related Hepatic Disorders Comprehensive Search SMQ, was 2.1% in the mirabegron 50 mg group, 2.3% in the mirabegron 100 mg group and 1.8% in the tolterodine ER 4 mg group. Most hepatic TEAEs were mild or moderate in intensity.
 - One patient in the mirabegron 50 mg group met laboratory criteria for Hy’s law; this patient had ongoing hepatitis B and a history of alcoholism. The case was ruled out as a confirmed case of Hy’s law due to the ongoing viral hepatitis as an alternate etiology.
 - The incidence of patients with hepatic parameters meeting PCS criteria was 1.0%, 1.3% and 0.9% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively (excluding patients who met the PCS criterion for isolated elevations in GGT only). The incidence of hepatic events based TEAEs and/or meeting hepatic PCS criteria (excluding events/elevations in GGT only) was 2.6%, 3.3% and 2.2% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively.
 - Changes in hematology and serum chemistry parameters, including renal parameters, were small and consistent across treatment groups except for leukocyte count.
 - In both mirabegron groups a decrease in leukocyte counts was observed at month 1 and month 6 but was followed by an observed increase for subsequent

measurements. The number of patients with an ANC < 1000 x 10⁶/L was comparable between treatment groups.

- Dose-dependent increases in adjusted mean change from baseline to Final Visit for AM and PM pulse rates were observed in all treatment groups (AM: 0.9, 1.6 and 1.5 bpm; PM: 0.4, 1.3 and 1.9 bpm for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively).
- For SBP, the adjusted mean changes from baseline to Final Visit for the mirabegron 50 mg group, mirabegron 100 mg group, and tolterodine ER 4 mg group respectively, were 0.2, 0.4 and -0.5 mm Hg for AM SBP and -0.3, 0.1 and -0.0 mm Hg for PM SBP. For DBP, the adjusted mean changes from baseline to Final Visit for the mirabegron 50 mg group, 100 mg group and tolterodine ER 4 mg groups, respectively, were -0.3, 0.4 and 0.1 mm Hg for AM DBP and -0.0, 0.1 and 0.6 mm Hg for PM DBP.
- Across the mirabegron and tolterodine treatment groups, increases in heart rate noted on ECGs were consistent with increases in pulse rate. No consistent ECG trends were identified.

Reviewer's Comment: In general, mirabegron appeared to be well tolerated in this study, the safety results for mirabegron were consistent with previous studies, and the overall safety profile was not notably worse for mirabegron compared to tolterodine. There is a small, but notable, increase in pulse and blood pressure with mirabegron and with tolterodine. The occurrence of hypertension in this study regardless of treatment arm was most likely to occur in the first three months. There is an increase in reports of neoplasm SAEs in the mirabegron 100 mg group compared to mirabegron 50 mg and to tolterodine.

Figure 5: Patient Disposition Study 178-CL-049



Source: Figure 2, Study Report 178-CL-049, page 78

Reviewer's comment: The discontinuations due to AEs and due to lack of efficacy were infrequent and comparable across groups.

Table 39: Overall Incidence of Treatment Emergent Adverse Events

Parameter n(%)	Mirabegron		Tolterodine ER 4 mg n=812
	50 mg n=812	100 mg n=820	
Adverse Events	485 (59.7)	503 (61.3)	508 (62.6)
Deaths	2 (0.2)	0	2 (0.2)
Serious Adverse Events	45 (5.2)	51 (6.2)	44 (5.4)
Adverse Events Leading to Study Discontinuation	48 (5.9)	50 (6.1)	46 (5.7)

Source: Table 18: Study Report 178-CL-049

Hypertension (based on PT) was the most frequently reported TEAE across all treatment groups (likely due to the prespecified definition in the protocol and instructions given to site investigators for reporting events of hypertension), with similar incidence in the mirabegron 50 mg group (9.2%), mirabegron 100 mg group (9.8%) and tolterodine ER 4 mg group (9.6%).

Table 40: Common ($\geq 2\%$ of Patients in any Treatment Group) Treatment Emergent Adverse Events Study 178-CL-049

MedDRA (v9.1) Preferred Term n(%)	Mirabegron		Tolterodine ER 4 mg n=812
	50 mg n=812	100 mg n=820	
Hypertension	75 (9.2%)	80 (9.8%)	78 (9.6)
Urinary Tract Infection	48 (5.9%)	45 (5.5%)	52 (6.4)
Nasopharyngitis	32 (3.9%)	35 (4.3%)	25 (3.1)
Headache	33 (4.1%)	26 (3.2%)	20 (2.5)
Back Pain	23 (2.8%)	29 (3.5%)	13 (1.6)
Constipation	23 (2.8%)	25 (3.0%)	22 (2.7)
Influenza	21 (2.6%)	25 (3.0%)	28 (3.4)
Dry Mouth	23 (2.8%)	19 (2.3%)	70 (8.6)
Sinusitis	22 (2.7%)	18 (2.2%)	12 (1.5)
Diarrhea	15 (1.8%)	24 (2.9%)	16 (2.0)
Arthralgia	17 (2.1%)	19 (2.3%)	16 (2.0)
Dizziness	22 (2.7%)	13 (1.6%)	21 (2.6)
Cystitis	17 (2.1%)	11 (1.3%)	19 (2.3)
Tachycardia	8 (1.0%)	19 (2.3%)	25 (3.1)

Source: Table 19, Study Report 178-CL-049, page 111.

Reviewer's Comment: Headache, nasopharyngitis, sinusitis, and back pain occurred at a greater incidence than in the tolterodine group.

Deaths:

Two treatment-emergent deaths occurred in the tolterodine ER 4 mg treatment group:

- One patient had a fatal AE of coronary artery disease on day 208 (last dose: day 208) which was not considered to be related to study medication by the investigator.
- One patient died on day 72 after experiencing fatal AEs of cerebrovascular accident and pneumonia aspiration which began on day 62. The last dose of study medication was on day 62. The events were not considered to be related to study medication by the investigator.

Two treatment-emergent deaths occurred in the mirabegron 50 mg treatment group.

- One patient died on day 108 after experiencing multiple organ failure secondary to sepsis with onsets of adverse events ranging from day 104 to day 107. Pneumonia was the only event considered to be possibly related to study medication. The last dose of study drug was unknown (estimated to be day 86).
- One patient had a fatal AE of cardiac failure on day 190 (last dose: day 190) which was not considered to be related to study medication.

Subject 1530-6120: The patient (a 64 year old white US female) randomized to 50 mg mirabegron developed a methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia on Day 108 that eventually progressed to sepsis, respiratory failure, multiple organ failure, disseminated intravascular coagulopathy, and death. The patient had a long-standing history of scleroderma and was taking plaquenil for rheumatoid arthritis. She had previously enrolled in Study 178-CL-047 and received placebo treatment.

The medical history included depression (unknown date), GERD (unknown date), hypertension (unknown date), paralysis (unknown date), peripheral vascular disease (unknown date), stress headaches (since 1950), partial hysterectomy (1975), intermittent constipation (since 1988), rheumatoid arthritis (since 1993), scleroderma (since 1993), osteoarthritis (since 1998), bilateral cataract surgery (2007), Raynaud's disease (since 2007-09), osteopenia (since 2007-09-28), and overactive bladder (since 2007-01-30). Her concomitant medications include hydroxychloroquine, acetylsalicylic acid, naproxen, and butalbital.

Reviewer's Comment: This subject suffered from both paralysis and scleroderma and had peripheral vascular disease which confound being able to associate the events in a causal manner to mirabegron.

Subject 3034-2380: The patient (a 72 year old white German female) with a long-standing history of diabetes mellitus and hypertension, experienced fatal cardiac failure on Day 190 during a vacation. She had been randomized to mirabegron 50 mg on 31 January 2009. The patient had been previously randomized to mirabegron 50 mg in Study 178-CL-046.

Her medical history included diabetes mellitus (since 1993), hypertension (since 1999), hysterectomy (1999), stomach ulcer (since 2005-04), and overactive bladder (since 2005-10). Her concomitant medications include: glimepiride, candesartan, nilvadipine, metformin, molsidomine and rabeprazole.

Autopsy results revealed chronic cardiac insufficiency as evidenced by severe coronary artery stenosis and pulmonary edema. The descending left anterior coronary artery was 80% stenotic. The subject had elevated blood urea nitrogen, creatinine, and glycosylated hemoglobin at screening and on day 28.

Reviewer's Comment: The patient had severe coronary artery stenosis, with documented 80% stenosis of the LAD. This pathology obviously pre-existed the clinical studies in which the patient participated. With this background condition, the role of mirabegron in the patient's fatal cardiac failure is unclear.

Reviewer's Comment: The two deaths that occurred in association with mirabegron 50 mg appear unrelated to drug therapy and do not generate a safety concern.

Patient 3063-3438 is classified as a non-treatment-emergent death (completed suicide). This death occurred in a mirabegron 50 mg-treated patient; the patient died on day 359, 93 days after the last study drug kit (containing 105 days worth of study drug) was dispensed. Using imputation rules (Statistical Analysis Plan: Appendix 13.1.9), the estimated last dose of study drug in this patient was Day 267. This death, therefore occurred beyond the 30 day post last-dose window for capture and is not included in the TEAE tables.

Table 41: Serious Treatment Emergent Adverse Events that Occurred in any SOC: Preferred Terms that Occurred in at Least 2 Patients in any Treatment Group

MedDRA (v9.1) System Organ Class Preferred Term	Mirabegron		Tolterodine ER 4 n=812
	50 mg n=812	100 mg n=820	
Any Serious Adverse Event	42 (5.2)	51 (6.2)	44 (5.4)
Neoplasms Benign and Malignant	1 (0.1)	11 (1.3)	5 (0.7)
Breast Cancer	0	2 (0.2)	2 (0.2)
Lung Neoplasm Malignant	0	2 (0.2)	0
Angina Pectoris	0	2 (0.2)	0
Cardiac Disorders	8 (1.0)	2 (0.2)	8 (1.0)
Atrial Fibrillation	2 (0.2)	0	3 (0.4)
Myocardial Infarction	1 (0.1)	0	2 (0.2)
Angina Pectoris	0	0	2 (0.2)
Gastrointestinal Disorders	3 (0.4)	7 (0.9)	2 (0.2)
Injury Poisoning and Procedural Complications	5 (0.6)	5 (0.6)	2 (0.2)
Surgical and Medical Procedures	2 (0.2)	7 (0.9)	2 (0.2)
Infections and Infestations	5 (0.6)	3 (0.4)	3 (0.4)
Musculoskeletal and Connective Tissue Disorders	3 (0.4)	5 (0.6)	2 (0.2)
Osteoarthritis	2 (0.2)	1 (0.1)	1 (0.1)
Nervous System Disorders	5 (0.6)	2 (0.2)	5 (0.6)
Cerebrovascular Accident	3 (0.4)	0	1 (0.1)
Reproductive System and Breast Disorders	3 (0.4)	4 (0.5)	8 (1.0)
Uterine Prolapse	0	2 (0.2)	0
Renal Urinary Disorders	1 (0.1)	5 (0.6)	3 (0.4)
Vascular Disorders	4 (0.5)	1 (0.1)	2 (0.2)
General Disorders and Administrative Site Conditions	3 (0.4)	1 (0.1)	2 (0.2)
Investigations	1 (0.1)	3 (0.4)	0
Liver Function Test Abnormal	0	2 (0.2)	0
Respiratory Thoracic and Mediastinal Disorders	2 (0.2)	1 (0.1)	1 (0.1)
Blood and Lymphatic System Disorders	1 (0.1)	1 (0.1)	1 (0.1)
Eye Disorders	1 (0.1)	1 (0.1)	1 (0.1)
Hepatobiliary Disorders	1 (0.1)	1 (0.1)	2 (0.2)
Cholelithiasis	0	1 (0.1)	2 (0.2)
Skin and Subcutaneous Tissue	1 (0.1)	1 (0.1)	0

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Ear and Labyrinth Disorders	0	1 (0.1)	0
Metabolism and Nutrition Disorders	1 (0.1)	0	2 (0.2)
Psychiatric Disorders	1 (0.1)	0	0

Source: Table 23, Study Report 178-CL-049, page 118

Reviewer's Comment: Considering the large size of this study and the 1-year duration, the number and incidence of SAEs shown in Table 41 are small.

A total of 17 reports of neoplasm were received as SAEs, most of these in the mirabegron 100 mg group. The types of neoplasms are heterogenous. Below is a summary table of the neoplasm SAEs:

Table 42: Study 178-CL-049 Serious Adverse Events of Neoplasms

Patient No/Age/Race/Sex/Country	MedDRA (v9.1) Preferred Term	Onset/Stop Day (Last Dose Day)	Treatment in Previous Study? (046/047/Naïve)	Additional Information: Adjudication
Mirabegron 50 mg				
2179-6744 54/White/Female/ US	Endometrial Cancer Stage I	315/350 (364)	Placebo (047)	Heavy vaginal bleeding x1yr: "Possible growth of preexisting neoplasm."
Mirabegron 100 mg				
1597-7875 61/White/Female/ US	Breast Cancer	86/Ongoing (294)	Mirabegron 100 mg (047)	Lesion noted Day 19 of Study
1651-8100 70/White/Male/ US	Prostate Cancer	54/Ongoing (58)	Mirabegron 50 mg (047)	Day 28 PSA 5.4 Day -162 PSA 3.49
2262-0172 52/White/Female/ Canada	Endometrial Cancer	139/216 (166)	Naive	Postmenopausal vaginal bleeding noted Day 83: "Possibly related to study drug but unlikely"
3016-1796 48/White/ Female/Germany	Hypopharynx Fibroma	329/332 (364)	Tolterodine SR 4 mg (046)	"Not related to either study drug and no prior evidence"

3016-1952 61/White/Female/ Germany	Lung Neoplasm Malignant	126/Ongoing (175)	Mirabegron 50 mg (046)	Presenting symptoms Day 97: “No evidence pre- existing, nor for study drug to growth and presentation”
3022-0128 69/White/Male/ Germany	Prostate Cancer	49/85 (82)	Naive	PSA 6.6 Day- 14: “Not related to study drug”
3025-2505 64/White/Male/ Germany	Pancreatic Carcinoma	323/376 (323)	Tolterodine SR 4 mg (046)	Initial symptoms Day 295: “possible but unlikely related. Role in tumor stimulation cannot be R/O”
3032-2166 69/White/Male/ Germany	Thyroid Neoplasm	263/269 (364)	Mirabegron 100 mg (046)	Path-no indication of malignant process: Worsening of lesion predated 046.
3034-2276 71/White/Female/ Germany	Breast Cancer	92 E (362)	Placebo (046)	Lesion on mammogram Day 92: “Too little time to cause lesion to be visible on mammogram”
3062-2853 58/White/Male/ France	Transitional Cell Carcinoma (bladder)	309/ongoing (308)	Placebo (046)	WBC & RBC (Day 30) in U/A for 4 mos: prior polypectomy, “stimulation of tumor growth by study drug cannot be R/O.”
3235-2623 74/White/Female/	Lung Neoplasm Malignant	53/ongoing (55)	Placebo (046)	Bronchitis noted Day-18:

Sweden				"Evidence for pre-existing"
Tolterodine ER 4 mg				
3013-0077 51/White/Female/ Germany	Breast Cancer	203/ongoing (370)	Naive	Dx routine mammography: "Possibility for tumor stimulation but no evidence of such."
3020-0298 60/White/female/ Germany	Breast Cancer Benign Lung Neoplasm	293/ongoing/(364) 300/ongoing/(364)	Naive	No prior mammogram
3020-0298 40/White/Female/ France	Uterine Leiomyoma	300/353 (364)	Tolterodine SR 4 mg (046)	Menorrhagia since 2007: "No evidence of enlargement of leiomyoma"
3235-1509 64/White/Female/ Sweden	Endometrial Cancer	296/ongoing/ (317)	Tolterodine SR 4 mg (046)	Post menopausal vaginal bleeding: "Bleeding could represent stimulation by study drug."

Source: Table 24, 178-CL-049 Study Report, page 118.

Herein all Neoplasm SAEs are provided as narratives:

Subject 2179-6744: Grade I Endometrial Cancer: The subject is a 54 year old white US female randomized to mirabegron 50 mg on [REDACTED] ^{(b) (6)}. The subject received a total of 364 days of study drug. The study treatment was not discontinued due to the adverse events. This subject previously participated in the 178-CL-047 study and was randomized to the placebo treatment group with the same assigned subject number. The subject received a total of 86 days of placebo. The medical history included obesity (since 1980), low back muscle spasms (since 1994), hypothyroidism (since 1998), anxiety (since 2002), depression (since 2002), hypercholesterolemia (since 2002), hypertension (since 2002), menopause (since 2006), menorrhagia (since 2008-10), pelvic pain (since 2008-10).

On day 315, serious adverse events of worsening of menorrhagia and endometrial Grade I cancer and a nonserious event of uterine fibroids were reported. There were no changes in study drug treatment for the events. The subject also had an adverse event of uterine fibroids reported on day 315. The subject had a relevant medical history of menorrhagia and pelvic pain since 2008-

10. Additional information revealed that the subject reportedly had continuous vaginal bleeding for over a year as well as pelvic pain and had not sought medical attention until an unspecified date in 2009-07. An adequate office examination at that time was impossible to do due to the subject's life-long history of sexual abstinence. A dilatation and curettage hysteroscopy was performed (exact date not known) that revealed inadequate, but benign-appearing endometrial tissue and a normal pap smear (discharge documentation).

On day 315, the subject was admitted to the hospital for surgical management. Physical examination on admission noted uterine fibroids. The subject underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and paraaortic lymphadenectomy. Pathology showed Grade I endometrial cancer with possible superficial invasion that measured more than 2 cm in greatest dimension.

Reviewer's Comment: The patient's symptoms pre-dated her participation in the mirabegron clinical studies. Thus, her endometrial cancer appears to have been an unidentified pre-existing condition.

Subject 1597-7875: Left Breast Cancer: The subject is a 61 year old white US female randomized to mirabegron 100 mg on [REDACTED] (b) (6). On [REDACTED] (b) (6), the subject initiated double-blind study drug therapy and received mirabegron 100 mg. The subject received a total of 294 days of study drug. The study treatment was not discontinued due to the adverse event. On day 294, the subject was withdrawn from the study for not meeting inclusion/exclusion criteria for the study (history of cervical cancer). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg treatment group. The subject received a total of 85 days of mirabegron 100 mg in that study. The medical history included appendectomy (1970), cervical cancer (1975), hysterectomy (1975-12), fibromyalgia (since 1980), allergy to penicillin (since 1986), breast biopsy (1988), myopia (since 1990), rheumatoid arthritis (since 1997), migraine cephalgia (since 2000-06-30), depression (since 2000-09), cholecystectomy (2001), osteopenia (since 2005-03-20), chronic hypokalemia (since 2006), hyperlipidemia (since 2006-12-05), degenerative disc disease (since 2007-01-19), osteoarthritis (since 2007-01-19), hypertension (since 2007-01-30), renal insufficiency (since 2007-03-14), tinnitus (since 2007-04-17), lumbar radiculopathy (since 2007-07-02), arteriosclerotic vascular disease (since 2007-10-31), anterior cervical fusion and anterior discectomy C 5-7 bilaterally (2007-12-14), insomnia (since 2008-01-09), cervical radiculopathy (since 2008-03-04), cataracts (since 2008-09-24). There is a past history of smoking of 2 packs per day with smoking cessation in 1999.

The subject had complained of enlargement of the right breast on day -1 [REDACTED] (b) (6). It was determined the changes in the right breast were due to fibrocystic changes. At the time of the subject's routine yearly mammogram (date unknown), a new irregular density of the left breast was noted. A biopsy was performed on day 66 that demonstrated an invasive ductal carcinoma (Grade II) with a tumor diameter of 0.6 cm. The Nottingham score was 6 (tubal formation 3, nuclear grade -2, mitotic activity -1). The mitotic rate was 1/10 HPF and the tumor was positive for estrogen and progesterone receptors by immunohistochemical staining. Perineural tumor invasion was present. On day 86, the serious adverse event of left breast cancer was reported. A sentinel lymph node biopsy performed on day 107 was negative. Chemotherapy was not

recommended. The subject was treated with 34 external beam radiation treatments which were completed on day 181. The adverse event of left breast skin blistering was reported (day 136 through day 181) and left mastalgia (day 136 through day 274). On day 183, the subject began treatment with anastrozole 1 mg daily for an indefinite period of time. The subject was withdrawn from the study on day 294 for not meeting inclusion/exclusion criteria for the study.

Reviewer's Comment: This patient's breast cancer was diagnosed after 85 days of mirabegron 100 mg therapy in Study 178-CL-049 followed by 66 days of mirabegron 100 mg therapy in this study.

Subject 1651-8100: Prostate Cancer: The subject is a 70 year old white US male randomized to mirabegron 100 mg (b) (6). The subject received a total of 58 days of study drug. The study treatment was discontinued due to the adverse event of prostate cancer on day 58 (b) (6). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group. The subject received a total of 83 days of mirabegron 50 mg in that study. The medical history included low back pain (since 1978), intermittent sciatica (since 1978), erectile dysfunction (since 1998), cerebrovascular accident (2002-03), benign prostatic hyperplasia (since 2002-09-01), carotid endarterectomy (2003), deviated septum repair (2004-01-12), vasectomy (2004-01-12), broken left hip (2005), surgery for fractured elbow (2005), surgery for right hip fracture (2005), shattered left elbow (2005), osteopenia (since 2005-05), bone grafting (2009-01-06), tooth removal, dental procedures and dental implants (2009-01-06) and oral pain (2009-01-06 through 2009-01-14). The subject was noted to have a past history of smoking ½ pack per day for 20 years.

On day 28, an adverse event of elevated prostate specific antigen (PSA) of 5.4 (units and reference range not provided) was reported. The subject was scheduled to have an ultrasound and biopsy. The ultrasound was remarkable for a prostate volume size of 45 cc. The results of the biopsy performed on day 54 were positive for prostate cancer and study drug was discontinued on day 58. The biopsy revealed Gleason 3 +3; positive from the right lateral apical area. Only 30% of the specimen was positive for cancer. There was no evidence of perineural invasion or extracapsular extension. On an unknown date, an additional biopsy revealed high-grade prostatic intraepithelial neoplasia (PIN) from the left medial base area. The subject was diagnosed with Stage II adenocarcinoma of the prostate, T1c NX MX. On day 54, the serious adverse event of prostate cancer was reported. The subject elected to pursue external beam radiation therapy utilizing image-guided radiation therapy (IGRT) and intensity modulated radiation therapy (IMRT) techniques, but postponed treatment for six months. The subject began marker placement on day 306 and radiation simulation for treatment on day 315.

Reviewer's Comment: Prior to entry into the 178-CL-047 study, the patient had a PSA of 3.49 ng/mL on Day -162. The Sponsor characterizes this pre-study PSA as elevated, which is arguable. This patient's prostate cancer was detected after 83 days of mirabegron 50 mg therapy in Study 047 followed by 54 days of mirabegron 100 mg therapy in this study.

Subject 2262-0172: Endometrial Cancer: The subject is 52 year old white Canadian female randomized to mirabegron 100 mg on [REDACTED] (b) (6). The subject received a total of 166 days of study drug. The study treatment was discontinued due to the adverse events of endometrial cancer and hysterectomy on day 166 [REDACTED] (b) (6). This subject did not participate in previous mirabegron studies. The medical history included allergy to penicillin (date not reported), sterility due to radiation (date not reported), hemorrhoids (since 1985-12-15), tonsillectomy (1988-01-01), non-Hodgkin's lymphoma (since 1996), radiation therapy (2000), herpes zoster (since 2000-04-12), depression (since 2000-11-15), anxiety disorder (since 2003-02-01), osteoarthritis (since 2006-06-01), sleep apnea (since 2007-01-20), frequent upper respiratory infection (since 2007-09) and chronic hypogammaglobulinemia (since 2008-09-03).

The subject had a relevant medical history of non-Hodgkin's lymphoma that had been treated with chemotherapy in 1996 and recurred in 2000; the recurrence was treated with a stem cell transplantation. The subject had no prior (before administration of study drug) symptoms related to the event and had no history of tobacco use.

An adverse event of vaginal bleeding was reported on Day 90. A transvaginal ultrasound was performed on day 98 [REDACTED] (b) (6) and showed a small nabothian cyst in the uterus and endometrial thickness of 1.5 cm. The ovaries were not seen and no free fluid was seen. On day 137, the subject presented to her family doctor with a vaginal burning sensation, a previous episode of postmenopausal spotting and a mild midline low abdominal pain which had been intermittent over the previous month. She was referred to a gynecologist for a biopsy and ultrasound. On an unspecified date, nuclear magnetic resonance (NMR) imaging demonstrated a mass 1.4 x 2.5 x 2.6 cm in the uterus. It did not appear to involve the myometrium or the cervix, but did involve the lower uterine segment. There was tethering of the rectum to the uterus. On day 139, endometrial cancer was diagnosed. On day 140, an endometrial biopsy showed a Grade 1 endometrial adenocarcinoma. On day 215, the subject was admitted to the hospital for a robotically-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy. The post-hysterectomy histology report revealed a primary tumor with less than 50% myometrial invasion, no cervix involvement, no venous/lymphatic invasion and positive involvement of the lower uterine segment. The margins were uninvolved by invasive carcinoma. The endometrium was completely filled by a yellow tan, friable mass measuring 3.2 cm x 2.8 cm from cornua to cornua.

Reviewer's Comment: This patient's approximate 3 x 3 cm endometrial cancer was detected secondary to symptoms that arose after 87 days of mirabegron 100 mg therapy.

Subject 3016-1796: Hypopharynx Fibroma: The subject is a 48 year old German female randomized to mirabegron 100 mg on [REDACTED] (b) (6). The subject received a total of 364 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR 4 mg treatment group. The subject received a total of 84 days of tolterodine in the previous study. The medical history included overactive bladder (since 2000).

On day 290, a serious adverse event of acute gastritis was reported. The subject had a 2-week history of decreased appetite and complained of nausea, headache and retrosternal burning on day 289. The subject had no relevant medical history; however, it was reported the subject had an increased ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) due to lumbar radiculopathy. The lumbar radiculopathy was described as prolapse of vertebral body 3/4, vertebral body lumbar 5/sacrum 1 protrusion and a degenerative narrowed spinal canal. An esophagogastroduodenoscopy was performed on day 293. During the EGD study, a 1-cm, flat, polyposis, space-occupying lesion within the pharynx was discovered. On day 329, a serious adverse event of hypopharynx fibroma was reported and the subject was hospitalized for removal of the hypopharynx fibroma detected during the esophagogastroduodenoscopy on day 293. A pathology report is not available.

Reviewer's Comment: Polyps of this type are almost always benign and known to be slow growing lesions. The patient's hypopharyngeal fibroma was discovered after 84 days of tolterodine in Study 046 followed by 364 days of mirabegron 100 mg in this study.

Subject 3016-1952: Lung Neoplasm Malignant: The subject is a 61 year old German female randomized to mirabegron (b) (6). The subject received a total of 175 days of study drug. The study treatment was discontinued due to the adverse event of lung cancer on day 175 (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg treatment group. The subject received a total of 89 days of study drug. The medical history included hysterectomy (1977), hypertension (since 2000) and hyperthyroidism (since 2000). The subject is a current smoker with a fifty pack year smoking history.

On day 126, a serious adverse event of lung cancer was reported. The subject experienced an adverse event of pneumonia that was reported on day 97 and was still ongoing at the time of the diagnosis of lung cancer. On day 126, the subject presented and was admitted to the hospital with a 4-week history of persistent pain on the right side of the chest and increasing dyspnea for 6 weeks. Sonography of the pleura showed a serous effusion without cavities on the right side. A bronchoscopy revealed visible signs of tumor tissue; no normal tissue was visible in the pulmonary lobe. A computed tomography scan showed a shadow in the right sinus maxillaris. A bone scan was recommended; this showed only scoliosis of the spine. An endoscopic ultrasound showed mediastinal enlarged lymph nodes at the level of lumbar vertebrae 4 and 7. Histological results from a sample at the base of the right pulmonary lobe showed a squamous cell carcinoma cT3 Nx (3), M(0) stage IIIB. Palliative chemotherapy was recommended.

Reviewer's Comment: The patient's lung cancer was detected after the patient had taken 89 days of mirabegron 50 mg therapy and 126 days of mirabegron 100 mg therapy. The patient had a history of smoking.

Subject 3022-0128: Prostate Cancer: The subject is a 69 year old white German male randomized to mirabegron 100 mg on (b) (6). The subject received a total of 82 days of study drug. The study treatment was discontinued due to the adverse event of prostate

carcinoma on day 82 (b) (6). This subject did not participate in previous mirabegron studies. The medical history included intervertebral disc prolapse (1999 and 2001), tinnitus (since 2006-11) and benign prostatic hyperplasia (since 2008). The subject is a nonsmoker.

On day 49, a serious adverse event of prostate carcinoma was reported. The subject had a relevant medical history of benign prostatic hyperplasia. On day 84, the subject was hospitalized and on day 85 underwent a radical prostatectomy without any complications. Additional source information has revealed that an elevated prostate specific antigen (PSA) value had been noted during a routine screening examination and at a follow-up assessment. The values were 6.6 mcg/L on day -14 (b) (6) and 6.64 mcg/L on day 30 (b) (6). A prostate biopsy on Day 44 confirmed prostate carcinoma in 2 of the 12 extracted punches, Gleason score 3+3. The histology revealed adenocarcinoma of the prostate in both lateral lobes, PT2c; no lymph vessel invasion, pL0; no blood vessel invasion, pV0; and tumor-free surgical resection margin marked in color, R0. The pathology report showed moderately differentiated adenocarcinoma of the prostate (Gleason score 3+3=6) and a tumor size of 25 mm. The tumor segment was < 5%, including tumor affect in both prostate lobes, with foci apical left and pronounced in the left transitional zone. There was no tumor infiltration of periprostatic fatty tissue and no evidence of lymph or hemangioma invasion. Focal tumor affecting the perineural sheaths was noted. The resection was surrounded by healthy tissue. The rest of the prostate tissue showed isolated foci of prostatic intraepithelial neoplasia (high-grade PIN) and signs of myoglandular prostate hyperplasia, urothelium of the prostatic urethra without dysplasia, and tumor-free normally structured seminal vesicles and spermatic duct.

Reviewer's Comment: The patient had an elevated PSA (6.64 ng/mL) prior to initiating mirabegron treatment in this study. The PSA was unchanged after 30 days of treatment with mirabegron 100 mg. The tumor was finally detected after 44 days of mirabegron 100 mg therapy. The elevated PSA at baseline suggests that the patient's prostate cancer was an unidentified pre-existing condition.

3025-2505: Pancreatic Carcinoma: The subject is a 64 year old German male randomized to mirabegron 100 mg on (b) (6). The subject received a total of 323 days of study drug. The study treatment was discontinued due to the adverse event of carcinoma of the head of the pancreas on day 323 ((b) (6)). This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. The subject received a total of 77 days of tolterodine in that study. The medical history included hypertension (since 1998) and hyperlipidemia (since 2000). The subject is a nonsmoker.

On day 323, a serious adverse event of carcinoma of the head of the pancreas was reported. The subject had no relevant medical history. The subject presented with malaise and icterus in the month prior to the event. On unspecified dates, ultrasonography, computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) were performed. As a result of these evaluations, the subject was diagnosed with pancreatic carcinoma on day 323. The subject was hospitalized on day 336 and resection of the head of the pancreas was performed on day 337.

Reviewer's Comment: On Day 295, the patient developed symptoms that ultimately led to the diagnosis of pancreatic cancer. The patient received 77 days of tolterodine in Study 046, followed by 323 days of mirabegron 100 mg in this study.

3032-2166: Thyroid Neoplasm: The subject is a 69 year old white German male randomized to mirabegron 100 mg on [REDACTED] ^{(b) (6)}. The subject received a total of 364 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg treatment group. The subject received a total of 84 days of mirabegron 100 mg in that study. The medical history included strumectomy (excision of goiter) (1964), hypothyroidism (since 1968) and benign prostatic hyperplasia (since 2007-04-17). The patient did not have a history of tobacco use.

On day 263, a serious adverse event of recurrent struma (goiter) with cold lump (thyroid cold nodule) was reported. The presenting symptoms which led to the diagnosis were increasing thyroid nodule and thyroid size, increasing thyroid hormone level and increasing dyspnea. These symptoms were present prior to drug exposure in Study 178-CL-049. Relevant medical history included a previous strumectomy (excision of goiter) in 1964 and hypothyroidism since 1968. The subject was admitted to the hospital and underwent a thyroidectomy with operative neuromonitoring on an unspecified date. There were no changes to the concomitant medication or study treatment dose due to this event. The parathyroid hormone level was 24.4 pg/ml (normal range 12 to 88 mmol/L). The histology report showed multinodal modification of the thyroid tissue concurrent with a recurrent goiter. There was no indication of a malignant process; however, because of intraoperative loss of neuromonitoring signal on the right side, the surgery was ended prematurely. Both lobes of the prostate had cold nodules on preoperative scanning. This finding continues to be an indication for left lobe thyroid surgery to rule out carcinoma.

Reviewer's Comment: The patient had goiter and thyroid surgery prior to receiving mirabegron in studies 178-CL-046 and 178-CL-049. The histology of the resected specimen was benign multinodular thyroid tissue. Additional resection is anticipated.

Subject 3034-2276: Breast Cancer: The subject is a 71 year old German white female who was randomized to mirabegron 100 mg on [REDACTED] ^{(b) (6)}. The subject received a total of 362 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment group. The subject received a total of 89 days of placebo in that study. The medical history included stomach ulcer (1983), vagotomy (1987), biopsy of left breast (benign results) (1997), hypercholesterolemia (since 2005), bilateral renal cyst (since 2008-03-05) and hypertension (since 2008-09-16). The subject was noted to have a prior history of smoking. Previous use of hormonal products is unknown.

The subject had a screening mammogram (date provided as day 92 in Adjudication Listing) and was hospitalized on day 118 [REDACTED] ^{(b) (6)} for histological clarification of a suspected focus in

the right breast. A punch biopsy was performed on an outpatient basis and the histological results showed a B2-lesion of the right breast. On day 119 [REDACTED]^{(b) (6)}, an excisional biopsy was performed and showed a well-differentiated, invasive ductal carcinoma of the breast (right, upper, outside). The carcinoma was characterized as G1, pT1b, L0, V0, R1, receptors positive and Her-2/neu negative. On day 138 [REDACTED]^{(b) (6)} the subject was re-hospitalized for follow-up resection and planned removal of sentinel lymph nodes. The histological assessment showed breast tissue with varying degrees of fibrosis of the stroma, moderate lymphoplasmacytic inflammatory infiltrate and formation of a fibrocystic mastopathy with some dilated duct sections and reactive epithelial hyperplasia. There were small foci of adenosis and additional apocrine metaplasia in individual sections. The secondary material including 14 lymph nodes were tumor-free with no evidence for metastasis. The subject was hospitalized a second time from day 138 through day 144 for a right breast resection and lymphadenectomy. The subject received radiation to the right axilla from day 179 through day 216 for a total of 28 treatments. Concomitant treatment included tamoxifen orally at a daily dose of 20 mg. There was no change to the study treatment dose as a result of this event. The subject received 28 courses of radiation therapy from day 179 to day 216 ([REDACTED]^{(b) (6)}).

Reviewer's Comment: This patient's breast cancer was detected on Day 92 of Study 049. In the previous study 046, she received 89 days of placebo.

Subject 3062-2853: Transitional Cell Carcinoma: The subject is a 58 year old French male randomized to mirabegron 100 mg on [REDACTED]^{(b) (6)}. The subject received a total of 308 days of study drug. The study treatment was discontinued due to the adverse event of urothelial carcinoma on day 308 [REDACTED]^{(b) (6)}. This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment group. The medical history included thyroid gland nodule resection (1993), type 2 diabetes (since 1998), chronic penile pain (since 2001), urinary bladder polyp (2003) and intra-ocular hypertension (since 2005). A smoking history is not provided in the narrative.

On Day 309, a serious adverse event of urothelial carcinoma was reported and the subject was hospitalized. Relevant medical history included bladder polyp resection in 2003 and diabetes mellitus since 1998. The subject had been experiencing aseptic leukocyturia and hematuria for approximately 4 months. (Urinalysis performed on Day 30 [REDACTED]^{(b) (6)}] and Day 175 [REDACTED]^{(b) (6)} [REDACTED] had showed hematuria.] It is to be noted that the subject experienced a urinary tract infection Days 3-9. Due to the laboratory anomalies in the urine, a cytologic study was requested on Day 227 [REDACTED]^{(b) (6)} and showed the presence of abnormal cells and increased red blood cells. A urinalysis revealed atypical urinary cells and a decision was made to perform a cystoscopy. The subject was found to have a bladder polyp that was resected and the pathology showed urothelial carcinoma. The impression of this was minimal pT1 stage of invasive transitional carcinoma, moderately to slightly differentiated (G-3) Her2/neu+++ . Screening for associated in situ carcinoma was negative. The subject was treated with endovesical BCG instillations beginning on approximately day 321 [REDACTED]^{(b) (6)}. The treatment was to consist of weekly instillations of 81 mg BCG for 6 consecutive weeks.

Reviewer's Comment: The patient had a distant prior history of bladder polyp resection, as well as a recent history of WBCs and RBCs in the urine. On Day 3, the patient experienced a urinary tract infection. Atypical cells were noted in the urine on Day 227 on urine cytology, and on Day 309, urothelial cancer was reported. The patient received placebo in the previous study 046.

Subject 3235-2623: Lung Neoplasm Malignant: The subject is a 74 year old Swedish male randomized to mirabegron 100 mg (b) (6). The subject received a total of 55 days of study drug. The study treatment was discontinued due to the adverse event of lung cancer on day 55 (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment group. The medical history included use of tobacco (1952 through 2008-09), gonarthrosis (knee arthritis) (since 1990), mood disorder (since 2004) and bronchitis (since 2009-01).

On day 53, a serious adverse event of lung cancer was reported. The subject had a relevant medical history of bronchitis and tobacco use. A pulmonary x-ray and nuclear magnetic resonance imaging (MRI) performed on unspecified days in (b) (6), and a bronchoscopy performed on an unspecified day in (b) (6) all showed evidence of a tumor. On an unspecified day in (b) (6), the subject was diagnosed with lung cancer. No concomitant medication was given for the indication of lung cancer. Study drug was discontinued due to this event on day 55. Treatment with radiochemotherapy was planned.

Reviewer's Comment: The patient was a smoker with a prior history of bronchitis. Less than 1 month after beginning treatment in study 049, a chest X-ray and MRI were performed and these tests led to a bronchoscopy in Month 2. On Day 55, the patient was diagnosed with lung cancer. The patient received placebo in the previous study 046.

Subject 3013-0077: Breast Cancer: The subject is a 51 year old German female randomized to tolterodine SR 4 mg on (b) (6). The subject received a total of 370 days of study drug. The study treatment was not discontinued due to the adverse event. This subject did not participate in previous mirabegron studies. The medical history includes arterial hypertension (since 2005-01). A history of tobacco use and use of hormonal treatments was unknown.

On day 203, a serious adverse event of breast carcinoma on the right side was reported. The tumor was diagnosed on routine mammography. There were no findings on inspection or palpation. The subject had a biopsy on day 203 (biopsy information not available). There was no evidence of metastatic disease. She was hospitalized on day 223 and underwent surgery of the right breast, with axillary dissection, on day 224. A positive sentinel node biopsy resulted in the axillary dissection. The histology report noted invasive ductal, primarily tubular, differentiated mammary carcinoma with a marginal intraductal component. The tumor was classified as pT1b (10 mm), pN1a (1/15, of those 2 sn), M0 G1 L0 V0 R0 (minimal resection margin of 6 mm), ER: 80% (IRS: 9) positive, PR: 10% (IRS: 6) positive, CerbB2: +++ positive. The subject was

discharged from the hospital on day 231 and treatment with tamoxifen was initiated. No changes were noted in the study drug due to this event.

Reviewers Comment: The patient's breast cancer was discovered during routine health screening after 203 days of study drug treatment. The patient did not participate in a previous mirabegron clinical study.

Subject 3020-0298: Breast Cancer: Hamartochondroma Lung: The subject is a 60 year old German female randomized to tolterodine SR 4 mg on [REDACTED]^{(b) (6)}. The subject received a total of 364 days of study drug. The study treatment was not discontinued due to the adverse event. This subject did not participate in previous mirabegron studies. The medical history included hysterectomy (1989), colposuspension (1998) and tension free vaginal tape (2005-12). The subject had no history of tobacco use and had undergone a hysterectomy in 1989 due to cervical carcinoma. The subject had no history of prior use of estrogen or birth control pills and reportedly had no history of prior mammogram abnormalities; however, extirpation of a microcalcification in the right breast in 2002 was noted in the hospital records. There was no family history of breast cancer

On day 293, a serious adverse event of cancer of the right breast was reported and on day 300, a serious adverse event of hamartochondroma in the right lung was reported. A lesion in the right breast was originally noted on a routine mammogram (date not specified) and sonography (date not specified) and mammography indicated a suspected focus of the right breast between the upper quadrants measuring 5 mm; the lesion was not palpable. On day 293, a punch biopsy of the right breast was performed and showed an invasive tubular carcinoma. A sentinel node biopsy was also performed and a tumor-free lymph node was observed intra-operatively. The subject was hospitalized on day 302 and underwent resection of the right mammary (breast) carcinoma with right axillary lymphadenectomy on the same day. Histologic examination revealed hamartochondroma. The tumor was classified as pT1a, pN0 (0/2), L0 V0 MX G1, estrogen IRS: 12, progesterone IRS: 0, HER2-Neu: 1+.

On day 300, prior to breast surgery, a chest x-ray was performed and findings were not clear. A computed tomography (CT) of the thorax was done on day 306 and revealed a suspicious intrapulmonary, space consuming lesion (approximately 1.2 cm) on the right upper lung field, discrete effusion in the pleura on the left side and small lymphatic nodes in front of the trachea with no pathological changes and no inflammatory infiltrates. Due to the incidental finding of pulmonary nodules, the subject was hospitalized on day 342. Bronchoscopy on Day 343 was normal. A thoracoscopic wedge resection of the right lung was performed on day 348 along with the small nodules noted. Pathology report showed localized hamartochondroma.

Reviewers Comment: The patient's breast cancer was detected after 293 days of treatment with tolterodine SR in this study. On Day 300, in preparing for breast surgery, a small tumor of the right lung was detected on chest x-ray. This tumor was confirmed by chest CT scan, and by subsequent wedge resection of the right lung. The lung tumor was a hamartochondroma, a very slow growing tumor

Subject 3068-3245: Uterine Leiomyoma: The subject is a 40 year old French female randomized to tolterodine ER 4 mg on [REDACTED] (b) (6). The subject received a total of 363 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group with the same assigned subject number. The subject received a total of 90 days of tolterodine SR in that study. The medical history included urethroplasty (1989), dysmenorrhea (since 2007-05-23) and menorrhagia (since 2007-05-23). The subject had no known history of tobacco use.

On day 85, a serious adverse event of uterus polomyomia was reported. The subject had a relevant medical history of urethroplasty and a fibromatous uterus that caused dysmenorrhea and menorrhagia. The subject was hospitalized on day 148 for a planned vaginal hysterectomy on day 149. The primary clinical which led to the diagnosis was menorrhagia since 2007 which worsened on Day 85. Histology report revealed a dystrophic endometrium with polyps, partially secretory with interstitial leiomyoma measuring 5.5 cm in diameter and another measuring 2 cm in diameter. The subject's uterus had a total weight of 300 grams.

Reviewer's Comment: The patient reported a history of dysmenorrhea, menorrhagia and a fibromatous uterus prior to initiating treatment in these studies. The patient had menorrhagia for 2 years prior, and this worsened after 85 days of treatment (with tolterodine SR) in Study 049. The patient had received 90 days of tolterodine SR in the previous study 046.

Subject 3253-1509: Endometrial Cancer: The subject is a 64 year old white Swedish female randomized to tolterodine ER 4 mg on [REDACTED] (b) (6). The subject received a total of 317 days of study drug. The study treatment was discontinued due to the adverse event of endometrial cancer on day 317 [REDACTED] (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. The subject received a total of 83 days of study drug. The medical history included arthritis (since 1991), hypothyroidism (since 1993), menopause (since 1995) and tension-free vaginal tape surgery (2000). The subject had no history of tobacco use and had not used hormone replacement therapy within 5 years of the diagnosis of endometrial cancer.

On day 238, a serious adverse event of post menopausal vaginal bleeding was reported. On day 281, after an endometrial biopsy, the pathologist reported a suspicion of endometrial cancer. On day 296, a uterine dilatation and curettage was performed and the subject was diagnosed with endometrial cancer. This event of endometrial cancer was reported as a serious adverse event. the subject underwent a hysterectomy with bilateral salpingo-oophorectomy on day 329 [REDACTED] (b) (6). Pathology of the uterus post hysterectomy revealed a highly differentiated adenocarcinoma of the endometrium (stage 1); it was reported that no pelvic lymph nodes were involved.

Reviewer's Comment: The patient experienced vaginal bleeding after 238 days of treatment with tolterodine SR in this study. On Day 296, endometrial cancer was diagnosed. The patient had received 83 days of tolterodine SR in the previous study 046.

Table 43: Summary of Neoplasm Relative Risk (by Dose Group and all Mirabegron Subjects) Versus Tolterodine in Study 178-CL-049

	Mirabegron 50 mg (N=812)	Mirabegron 100 mg (N=820)	Mirabegron combined (N=1632)	Tolterodine ER 4 mg (N=812)
All neoplasms	n=1 RR=0.25 95% CI (0.03, 2.23) p =0.3742	n=11 RR=2.72 95% CI (0.87, 8.52) p=0.1168	n=12 RR=1.49 95% CI (0.48, 4.61) p =0.6008	n=4
Malignant neoplasms	n=1 RR=0.33 95% CI (0.03, 3.20) p =0.6245	n=9 RR=2.97 95% CI (0.81, 10.93) p =0.1446	n=10 RR=1.66 95% CI (0.46, 6.01) p=0.5630	n=3
Malignant neoplasms on same drug, naïve or placebo in pivotal studies	n=0 p=0.2495	n=5 RR=1.65 95% CI (0.40, 6.88) p=0.7259	n=5 RR=0.83 95% CI (0.20, 3.46) p=0.4526	n=3
Malignancy neoplasms arising after 90 days of cumulative exposure to drug (includes pivotal studies)	n=0 p=0.2495	n=5 RR=1.65 95% CI (0.40, 6.88) p=0.7259	n=5 RR=0.83 95% CI (0.20, 3.46) p=0.4526	n=3

n: number of patients RR: relative risk vs tolterodine ER CI: confidence interval p: P-value from Fisher’s exact test

Sources: Table 41 and computations performed by Office of Biometrics

On January 30, 2012, the Division received a final consultation from the Division of Oncology Products. The consultants made the following observations based on questions posed by DRUP:

- Upon review and examination of the submitted adverse event dataset and the review of the study report on neoplasms identified during the trial, the consultant found that the number of neoplasms reported as an SAE was accurately reflected in the study report.
- The submitted narratives show that all the serious neoplasms, except for Case 3016-1796 (fibroma), were supported by pathological evidence and cannot be excluded. The consultant agreed with the Adjudication Committee’s case by case analysis of neoplasms in Study 178-CL-049.
- The recommended dose for the proposed indication is 50 mg mirabegron once daily which had the lowest incidence of neoplasms in the three study arms.
- The consultant is not aware of a similar clinical situation in which the incidence of neoplasms was found responsive to a 2-fold increase in dose (50-100 mg mirabegron).

- While the 100 mg mirabegron dose once daily is not recommended in the draft product label, the increased number of neoplasms in the mirabegron 100 mg group was still of some concern.
- The consultant does not recommend pooling the data from the mirabegron 50 mg and 100 mg groups in Study 049 to compare with the control arm, for the following reasons:
 - 5 of 11 neoplasm SAEs in the mirabegron 100 mg group were diagnosed within 12 weeks of study treatment and 2 of the 11 diagnosed were diagnosed between Months 3-6 of the treatment initiation. The remaining 4 cases, including the case of fibroma, were found between months 6-12 of the trial. This is comparable to the time course of the neoplasms found in the tolterodine arm.
 - In the four 12-week Phase 3 trials of the product, a remarkable imbalance of malignancies was not found; however, the consultant notes that in the 1-year study, 5 of 11 cases occurred within the first 12 weeks.
 - The detected neoplasms were heterogeneous in tissue of origin.
- There is no apparent relationship between prior exposure and neoplasm detection in Study 049. The significance of previous exposure to mirabegron, tolterodine, or placebo is difficult to estimate.
- The consultant did not find a remarkable imbalance in the incidence of neoplasms among the four 12-week phase 3 studies (includes non-NDA Japan study) of the product.
- The consultant recommended no additional analyses. The need for further studies could be discussed at the Advisory Committee meeting.

Reviewer's Comment: The gender distribution of the 17 neoplasm subjects is 5 male and 11 females which mirrors the sexual distribution of all subjects enrolled in Study 178-CL-049. Of the 17 neoplasm subjects three were from the US, eight were from Germany, two were from France, two were from Sweden, and one was from Canada. The tumors represent the most common tumors occurring in most populations. There is no common mechanism that can explain these tumors. If the tumors arising in the mirabegron 50 mg group and the mirabegron 100 mg are totalled (pooled) and divided by the total number of mirabegron subjects, the neoplasm incidence would roughly equal that in the tolterodine group.

Many, and perhaps all, of the neoplasm noted in Study 178-CL-049 were preexisting lesions. Currently, there is no common mechanistic rationale to implicate mirabegron in these cancers. It is not possible, though to fully exclude a role of mirabegron in these events, at the 100 mg dose. A postmarketing study might be helpful in further elucidating a role, if any, for mirabegron in these events.

Additional Selected SAE Narratives in Brief (the following cases were selected for presentation based upon their potential relevance to the safety of mirabegron, cases from the tolterodine group are not shown):

Mirabegron 50 mg:

Subject 1530-6120: Death: Sepsis: Multiorgan Failure: See discussion under deaths.

Subject 1534-7502: Diverticulitis: The subject is a 59 year old white US female randomized to mirabegron 50 mg. She has a past history of hypertension, hypercalcemia (since 2000), chronic obstructive pulmonary disease, gastric banding and diverticulitis (since February 2008). The patient was noted to have elevation of hematocrit, hemoglobin and neutrophils (17 November 2008 through 15 January 2009).

Reviewer's Comment: This appears to be a recurrence of a pre-existing condition.

Subject 1630-6370: Hip Fracture, Pelvic Fracture: The subject is a 61 year old white US female randomized to mirabegron 50 mg (b) (6). The subject received a total of 222 days of study drug. The study treatment was discontinued due to the adverse events of left hip fracture and pelvic fracture. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg treatment group.

The medical history included heart murmur (since 1950), rheumatic fever (1950), allergy to codeine (since 1957), obesity (since 1971), left femoral fracture (1998 through 1998-01), allergy to Dilaudid (since 1999), osteoporosis (since 1999), metal plate screwed to femur (1999-09), left tibia and fibula fracture (2000-02), metal plate screwed to tibia and fibula (2000-09), arthritis (since 2002), benign colon polyp excision x2 (2002 and 2007), menopause (since 2003), fractured left humerus (2005-12), environmental allergies (since 2007), hyperlipidemia (since 2007), itchy eyes (since 2007), trigger finger of the right middle finger (since 2008), head cold (2008-09-11 through 2008-09-13), and overactive bladder (since 1998). The medications she was taken at the time of the acute event include: calcium, naproxen, ascorbic acid, magnesium, ergocalciferol, loratadine, alendronic acid.

On day 222, the subject reportedly slipped and fell at home on a wet floor that she was washing and was admitted to the hospital. Pelvic x-rays revealed an acute comminuted fracture of the left acetabulum. CT of the pelvis revealed a displaced severely comminuted fracture of the left acetabulum involving the anterior and posterior columns with the fracture line extending through the iliac wing and fractures of the left inferior pubic ramus and at the junction of the left pubic bone and superior pubic ramus. CT angiogram of the abdomen revealed an aneurysmically dilated atherosclerotic abdominal aorta without evidence of aortic dissection.

The subject had a transthoracic echocardiogram which showed normal sized left ventricular cavity. Due to suboptimal technical quality, a focal wall motion abnormality could not be fully excluded. Left ventricular systolic function was normal (ejection fraction 55%) and right ventricular chamber size and free wall motion was normal. The aortic valve was not well seen and there was no aortic valve stenosis or aortic regurgitation. The mitral valve leaflets were mildly thickened and physiologic mitral valve regurgitation (within normal limits) was seen. The tricuspid valve leaflets were mildly thickened. The pulmonary artery systolic could not be determined and there was no pericardial effusion. A dipyridamole-sestamibi test showed probable moderate reversible basal inferior wall defect with normal systolic function and cavity size. There were no ECG changes.

Reviewer's Comment: This subject had osteoporosis with previous tibia/fibula and femur fractures and was taking alendronic acid. The subject accidentally slipped and fell while mopping a wet floor and sustained severe left hip and pelvic fractures complicated by acute blood loss requiring transfusions. There was no reported loss of consciousness, fatigue, or obtundation associated with this event. Cardiac function and ECG were normal.

Subject 1630-6566: Acute Myocardial Infarction: The subject is a 50 year old white US male randomized to mirabegron 50 mg (b) (6). The subject received a total of 365 days of study drug. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg treatment group. The medical history included right leg crushing injury (1976), obesity (since 1982), allergy to MSG (since 1994), headaches (1994 through 1995), GERD (since 1997), occasional heartburn (since 1997), right leg edema (since 2002), hypertension (since 2002), sphincter of Oddi sphincterectomy (2004), cholelithiasis (2004-03-03 through 2004-03-15), liver cysts (since 2004-03-03), pancreatitis (2004-03-03 through 2004-03-15), depression (since 2004-04-30), hyperlipidemia (2004-04-30 through 2008-01-25), degenerative joint disease of the right ankle (since 2004-09-22), constipation (since 2006), osteoarthritis (since 2007-06-28), venous insufficiency (since 2007-06-28), pinched nerve in back (since 2008-02-13), shoulder pain (since 2008-05-08), diverticulosis (since 2008-11-18). The concomitant medications patient was receiving at the time of the acute event were: calcium carbonate, ducosate, diclofenac, tramadol, and omeprazole.

On day 265, the subject presented to the clinic with mid-sternal chest discomfort at rest (an adverse event of angina pectoris was reported day 264 through day 265), slightly elevated cardiac enzymes, and ECG without ST changes. The subject was transferred by ambulance and admitted to the hospital for further management. Cardiac catheterization on day 266 revealed severe single vessel disease with 99% lesion of the proximal 1st diagonal of the left anterior descending artery. Overall, left ventricular function was normal. Echocardiogram revealed no regional wall abnormalities and an ejection fraction of 55%. The diagnosis was non-ST segment elevation myocardial infarction was reported. The patient's ECGs are reported as normal on study Days -14, 183, and 365. His baseline blood pressures home and office devices were 127/95 and 129/89 mmHg respectively. His 1 month, 3 month, 6 month, and 9 month office blood pressures were 124/85, 104/77, 120/83, and 129/78 mmHg respectively.

Reviewer's Comment: This patient had a medical history of smoking, obesity, hyperlipidemia, hypertension, and venous insufficiency as risk factors predisposing to coronary artery disease. Angiography demonstrated severe LAD disease with a 99% lesion of the proximal 1st diagonal branch. His blood pressures throughout the study were stable and normal.

Subject 1656-7207: Cerebrovascular Accident: The subject is a 60 year old black American female randomized to mirabegron 50 mg (b) (6). The subject received a total of 172 days of study drug. The study treatment was discontinued due to the adverse event of cerebrovascular accident on day 172. This subject previously participated in the 178-CL-047

study and was randomized to the mirabegron 100 mg. The medical history included asthma (since 1955), breast lumpectomy (1966), seasonal allergic rhinitis (since 1970), depression (since 1980), tubal ligation (1980), hypertension (since 1988), multiple sclerosis (since 1990), menopause (since 2004), arthritis of the shoulder (since 2005). Her concomitant medications at the time of the acute event (Day 97) are: salbutamol inhaler, fluoxetine, interferon beta-1B subcutaneous, diltiazem, hydrochlorothiazide/triamterene, hydrocodone/paracetamol, and lisinopril.

On day 97, the serious adverse event of cerebrovascular accident (CVA) was reported. A routine followup MRI on Day 79 was unchanged from prior studies. A CT head scan on Day 95 revealed an old lacunar infarct in the left caudate nucleus and scattered areas of ill-defined low density lesion in the white matter. On Day 96 the patient developed new neurologic symptoms of right leg paresthesias and weakness which progressed to cramping pain and drooling. A CT scan was unremarkable and she was treated with steroids in the emergency room and discharged. Upon return to the emergency secondary to persistence of symptoms, she developed lethargy and respiratory depression and was placed on BIPAP. During hospitalization, a 2 cm area in the right basal ganglia and right corona radiata showed evolving changes compatible with an acute or subacute infarct. A carotid ultrasound on Day 99 was normal. The patient ultimately recovered with residual left sided hemiparesis and dysphagia.

Reviewer's Comment: The patient had long-standing hypertension and was taking three anti-hypertensive medications at baseline. A CT scan of head was performed on Day 95 and showed an old lacunar infarct in the left caudate nucleus and left-sided areas of ill-defined low density lesion in the white matter. On Day 95, she presented with neurologic symptoms and had what was reported as an unremarkable head CT. She returned after developing respiratory depression and lethargy and a CT showed an acute or subacute right-sided infarct. The patient's previous cardiovascular and neurologic conditions could be contributory, but a causal association with mirabegron cannot be excluded.

Subject 1681-6947: Atrial fibrillation with ventricular response: bilateral pneumonia: The subject is an 82 year old white US female randomized to mirabegron 50 mg on (b) (6). The subject received a total of 237 days of study drug. The study treatment was not discontinued due to the adverse event. The subject withdrew consent and the last dose of study drug was on day 237. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg. The medical history included myopia (since 1965), depression (since 1975), menopause (since 1986), allergy to Demerol (meperidine) (since 1988), anxiety (1995 through 2006), bilateral cataract removal (1995), hypercholesterolemia (since 1998), hypothyroidism (since 1999), mitral valve prolapse (MVP) (since 1999), hypertension (since 2001), pericarditis (2001), bladder sling surgery (2003), left knee replacement (2003), right side of mesentery not attached (since 2003), Bell's palsy (2004), seasonal allergies (since 2004), arthritis (since 2005), stroke (2007-08), mild dementia (since 2008-02), non-ST elevation myocardial infarction (NSTEMI) (since 2008-07-02). Concomitant medications include a variety of health supplements (glucosamine, ascorbic acid, tocopherol, chondroitin,

methysulfonyl methane and polycarbophil), simvastatin, levothyroxine, venlafaxine, celecoxib, quinapril, acetylsalicylic acid, donepezil and meclizine.

On day 166, serious adverse events of atrial fibrillation with rapid ventricular response, bilateral pneumonia, and respiratory failure were reported. Study drug was interrupted on an unknown date for these serious adverse events. On this same day (day 166), an adverse event of increased dementia was reported. The patient was admitted to the hospital with acute respiratory failure. The ECG upon admission showed sinus bradycardia and right bundle branch block. A pulmonary angiogram showed no evidence of embolic disease. A chest x-ray show a possible infiltrate in the right and left lung and bilateral pleural effusions. While in hospital, the patient developed atrial fibrillation and respiratory failure. The atrial fibrillation converted to into normal sinus rhythm with treatment with digitalis, Cardizem and sotalol. The patient's pulmonary status improved. She recovered but required readmission due to recurrent *C. difficile* colitis.

Reviewer's Comment: Development of atrial fibrillation in the subject was likely secondary to hypoxia secondary to the primary pulmonary process of bilateral pneumonia; Baseline cardiac risk factors for atrial fibrillation included long-standing hypertension, levothyroxine use, advanced age, and probable baseline cardiac dysfunction suggested by a history of NSTEMI and MVP etiology for the presence of pulmonary effusions was likely excluded by the negative BNP level. It is unlikely that mirabegron is causally associated with the atrial fibrillation in this case, as pneumonia with hypoxia is a well-known association with atrial fibrillation. In light of a history of stroke, a causal association of mirabegron and pneumonia is also confounded.

Subject 2203-0424: Cardiac Arrest, Myocardial Infarction, Ventricular fibrillation and tachycardia: The subject is a 44 year old white Canadian female randomized to mirabegron 50 mg (b) (6). She had not participated in previous mirabegron studies. The subject received a total of 17 days of study drug. The study treatment was discontinued due to the adverse events of cardiac arrest, myocardial infarction, ventricular fibrillation and ventricular tachycardia on day 17 (b) (6). The medical history included allergies to dust mites, cats, dogs, trees, grass, weeds, feathers, pollen, clarithromycin, cephalexin, dairy, eggs, oatmeal, celery and chocolate (since 1970); bronchial asthma (since 1984), hysterectomy (1990), anxiety (since 1990), L3 and L4 disc compression (since 1995), left ankle fracture (1999), whiplash injury (since 2000), restless leg syndrome (since 2004), recurrent bilateral ear infections (since 2004), constipation (since 2005), depression (since 2006), cigarette smoking (2007 through 2009-03-20), cyst removed from left breast (2007), slight heart murmur (since 2007), hypertension (since 2008), bilateral ear surgery with tube insertion (2008-09-15). The patient's concomitant medications at the time of the event were: lorazepam, ropinirole, venlafaxine, and esomeprazole. There is a family history of cardiac disease, heart attack and stroke noted in the hospital record.

On Day 17, the subject collapsed in her home. A fire and ambulance service was called. The fire and ambulance service found the subject without a pulse and based on the cardiac consultation

records, the subject's rhythm strip revealed ischemic induced polymorphic ventricular tachycardia with no evidence of QT prolongation or Torsades (b) (6) cardiac consultation note). Emergency medical services defibrillated the subject, an electrocardiogram (ECG) conducted while en route to the hospital revealed sinus tachycardia and a pulse of 143 bpm. Following the successful defibrillation, the subject was in sinus rhythm with evidence of tombstone ST elevation in the anterior precordial leads extending into the high lateral leads. An ECG performed approximately 1 hour later in the emergency room showed that the ST segments were resolving to approximately 50% of the initial ST segment elevation. Lactic acid level was 8.9, bicarbonate was 13, anion gap was 17 and troponin was 0.063; no units or normal ranges were provided. Cardiac catheterization showed the coronary anatomy to be right-dominant and the proximal left anterior descending (LAD) artery showed 95% stenosis. The subject was given nitroglycerin. Despite some reversal, the underlying coronary artery stenosis remained. A drug-eluting stent was placed in the LAD artery. An ECG after the cardiac catheterization and stent placement showed resolution of the ST segment elevation.

A urine test on day 17 was positive for benzodiazepines and cannabinoids; the test was negative for methadone, cocaine, amphetamines, opiates, barbiturates and tricyclic antidepressants. The subject did not report a previous medical history of drug overdose, suicidal thoughts or substance abuse during the screening visit. The patient was also noted to have mitral and tricuspid valve regurgitation.

Reviewer's Comment: On angiography, the patient had 95% stenosis of the LAD, which did not reverse with nitroglycerin. The events were ischemic-induced resulting from coronary artery stenosis (catheterization revealed 95% stenosis of the LAD) and possible spasm. According to the cardiac consultation, the polymorphic ventricular tachycardia on presentation was not consistent with QT prolongation or Torsades de Pointes. It is unlikely that a causal association exists between the events and mirabegron. This patient was reported in the Torsade de Pointes/QT prolongation SMQ. In MedDRA 13.0, ventricular arrhythmias and cardiac arrest as a high level term are within the preferred term, Torsades de pointes. It was stated in the filing review on page 77 that this patient had torsades. That is incorrect. At no time was a prolonged QT noted in this patient. At the time of filing, the events in this case were a review issue. The review issue of possible torsades is now resolved.

Subject 3019-0364: Hypertension (worsening): The subject is a 46 year old white German female randomized to mirabegron (b) (6). The study treatment was discontinued due to the adverse event of worsening hypertension on day 2 (b) (6). The medical history included cholecystectomy (1996), hysterectomy (1999), hypertension (since 2004-05). Her concomitant medications at the time of the event include amlodipine, candesartan, and metoprolol.

On day 3, the subject was hospitalized due to a change in blood pressure and complaints of dyspnea, a thoracic feeling in her chest, anxiety and decreased vigor in the past weeks. Upon admission, the subject's blood pressure was 170/90 mmHg and her heart rate was 84 beats per

minute. An electrocardiogram (ECG) on day 3 revealed no change in comparison to an ECG performed on [REDACTED] (b) (6). The subject underwent an exercise ergometry evaluation on day 9; there were no pathological findings, and no signs of stenosis or coronary heart disease

The patient's vital sign averages were as follows:

Vital Signs Subject 3019-0364

Visit/Device	Blood Pressure (mmHg)	Heart Rate (bpm)
Day -21 Home	170.3/105.1	73
Day -12 Home	163.6/84am 159.3/85.7pm	86am : 82pm
Day -2 Home	177.6/81.3am 172.3/86pm	83am : 80pm
Day -1 Home	180/100am 176.7/93.3pm	73am : 70pm
Baseline Home	180/100	74
Baseline Office	177/92	70

Source: Patient narrative and CRF

Reviewer's Comment: The patient was seriously hypertensive at baseline, and was taking three anti-hypertensive medications. The blood pressure on Day 2 was not different from the baseline home or office blood pressures. Previous blood pressures prior to baseline indicate the control of the blood pressure was not optimized. The blood pressure was not worsened as compared to baseline readings.

Subject 3027-2475: Upper Limb Fracture: The subject is a 52 year old German male randomized to mirabegron 50 mg on [REDACTED] (b) (6). He received 358 days of study drug and was not discontinued to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg. The medical history included exanthema (2008-12-16 through 2009-01-30). The patient was taking cetirizine for exanthema at the time of the event.

On Day 134, the patient fell from his bicycle and accidentally fractured his shoulder. There are no reported nervous system changes indicative of impairment contributory to the accident.

Reviewer's Comment: I cannot attribute a causal association to mirabegron.

Subject 3027-2581: Femoral Neck Fracture: The subject is an 82 year old white German female randomized to mirabegron 50 mg on [REDACTED] (b) (6). The subject received a total of 293 days of study drug. The study treatment was discontinued due to the adverse event of femoral neck fracture on day 293. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. The medical history included coronary heart disease (since 1979), osteoarthritis (since 1984), cataract (since 2002), diabetes mellitus (2002 through 2007-09), hyperuricemia (since 2003). Concomitant medications include acetylsalicylic acid, allopurinol, tilidine, metoprolol, simvastatin, furosemide/spironolactone,

hydromorphone (for backache) and methocarbamol (for backache). On day 293, a serious adverse event of femoral neck fracture was reported. The subject was hospitalized and underwent total endoprosthesis (TEP) surgery. The details on the circumstances surrounding the event were unavailable.

Reviewer's Comment: There is not adequate information to allow a conclusion of a causal association of this SAE and mirabegron.

Subject 3030-1541: Intestinal Abscess (Colon): Cerebrovascular Accident: Atrial

Fibrillation: The subject is a 68 year old German female randomized to mirabegron 50 mg on (b) (6). The subject received a total of 99 days of study drug. The study treatment was discontinued due to the adverse event of colon abscess (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg. The medical history included hypertension (since 1998), depression (since 2006), osteoporosis (since 2006), rheumatism (since 2006-10), incontinence of anal sphincter (since 2008), and overactive bladder. Concomitant medications include prednisolone 2.5 mg a day, talinolol, and zopiclone.

On day 100, a serious adverse event of colon abscess was reported and the subject was hospitalized. On day 106, the subject underwent a resection of the colon abscess. The study treatment was discontinued due to this adverse event. The event was reported as resolved on day 106. The patient has no known history of diverticular disease but the colon abscess at surgery was found in association with diverticular disease.

On Day 113, the patient developed right hemiplegia and total aphasia. CT head imaging on Day 114 showed changes compatible with a left CVA. Upon admission to the stroke unit, the patient was found to be in atrial fibrillation (>100 bpm). Concomitant treatment included digoxin orally at a daily dose of 0.07 mg and potassium bicarbonate and potassium citrate 1 tablet, orally per day. An echocardiogram showed no pathological findings. No ECG or vital sign data were provided on admission to the stroke unit or during hospitalization. The baseline ECG, as well as blood pressure, and heart rate readings taken throughout the study were normal. A normal sinus rhythm was achieved with digoxin treatment.

Reviewer's Comment: In regard to the diverticular abscess, it is not possible to attribute the event to mirabegron. Diverticulosis is commonly found in the general population, and some diverticular disease does progress to symptomatic disease and/or abscess. I agree with Sponsor, that the recent (1 week prior) open abdominal surgery and given the subject's cardiac risk factors, including a longstanding hypertension, the events of stroke and atrial fibrillation may be coincidental findings and or post-surgical in etiology; however, a causal association to mirabegron cannot be completely excluded.

Subject 3034-2380: Cardiac Failure: This subject is discussed under Deaths.

Subject 3090-2687: Asthma: Bronchitis: The subject is a 68 year old Czech white female randomized to mirabegron 50 mg (b) (6). The subject received a total of 372 days of study drug. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group with the same assigned subject number. A narrative was written for this subject only because of the listed event of “planned diagnostic procedure-heart catheterization”. She has had bronchial asthma since 1970. Her concomitant medications at the time of the event were: fluticasone/salmeterol inhaler, isosorbide inhaler for angina, insulin glargine, insulin aspart, omeprazole for gastroesophageal reflux, carbidopa/levodopa for leg cramps, amlodipine for hypertension, and atorvastatin for hypercholesterolemia.

On day 8, a serious adverse event of bronchial asthma was reported and the subject was hospitalized for temporary worsening of asthma during an episode of bronchitis. On day 356, the subject was re-hospitalized for worsening asthma during bronchitis. The Sponsor states, “The subject was a known asthmatic and the events were exacerbated by bronchitis. The presentation was determined not to be a case of drug hypersensitivity.”

Reviewer’s Comment: This case is considered in brief as the patient has bronchial asthma for which an SAE of asthma was not reported in Study 178-CL-046 while she was taking tolterodine SR/ER 4 mg. She had two asthma attacks associated with bronchitis which the Sponsor determined not to be a case of drug hypersensitivity. These events could therefore be induced by bronchial infections that were treated with courses of antibiotics. In the first attack (Day 8), amoxicillin/clavulanic acid and in the second attack (Day 356), clarithromycin were administered.

Subject 3101-1683: Open Angle Glaucoma: The subject is a 52 year old Slovakian white female randomized to mirabegron 50 mg on (b) (6). This patient had a history of open angle glaucoma since 2007 and was under treatment. She was hospitalized on Day 98 to assess glaucoma status in light of worsened vision and headache. Her intraocular pressures were within the normal range. The Sponsor states there was no evidence of worsening glaucoma.

Reviewer’s Comment: In this patient with a history of open angle glaucoma under treatment, I cannot causally relate open angle glaucoma to mirabegron.

Subject 3101-2272: Urticaria: The subject is a 43 year old white Slovakian female randomized to mirabegron 50 mg on (b) (6). The study treatment was discontinued due to the adverse event of acute urticaria on day 33 (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment. The medical history included chronic gastritis (since 1998), gastric ulcer (1998), tinnitus (since 2004), vertebrogenic syndrome (since 2005). Concomitant medications at the time of the event were drotaverine for gastritis and ibuprofen.

On day 26, the subject was hospitalized and admitted to the dermatology department due to acute urticaria. The rash was described as pruritic, slightly raised, pink and red papules on the thighs, forearms and face. Additionally, the nail of the right big toe revealed a longitudinal strip with

Clinical Review

{Insert Reviewer Name}

{Insert Application Type and Number}

{Insert Product Trade and Generic Name}

crevices. On the right crus (lower leg) medially and dorsally, a nonhomogenous hemangioma was present. Varices were present bilaterally on the crus. On the second day of hospitalization (day 27), new eruptions of urticaria were reported on the belly and dorsal thighs. On the third day of hospitalization (day 28), the subject evidenced initial regression of the urticaria. There were no constitutional symptoms, changes in diet, food supplements or medications.

Laboratory examinations revealed a slightly increased sedimentation rate, and elevation of C-reactive protein (CRP) and total IgE levels. Pertinent negatives included no reported constitutional symptoms, eosinophilia or elevations in liver chemistries. The laboratories are shown in the scanned narrative tables below:

Table 2: Relevant Laboratory Results - Hematology

Study Day	Erythrocytes (normal range 3.68 – 5.09 10 ¹² /L)	Hemoglobin (normal range 116 - 154 g/L)	Hematocrit (normal range 0.34 – 0.45 fraction)	Leukocytes (normal range 3.6 – 10.0 10 ⁹ /L)	Eosinophils (normal range 0 – 480 10 ⁶ /L)	Platelets (normal range 145 – 390 10 ⁹ /L)
-20	4.44	139	0.40	6.20	290	197
33	4.45	138	0.40	5.45	210	184

Study Day	Alanine Amino transferase (ALT) (normal range 1 - 30 U/L)	Aspartate Amino transferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphatase (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 – 18.6 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 – 32 U/L)
-20	12	13	65	11.1	18
*26	0.21	0.22	1.00	9.8	0.38
33	17	14	63	4.8	21

* Hospital laboratory results – Laboratory normal range (ALT: 0.20-0.60 ukat/L; AST: 0.20-0.60 ukat/L; ALKP 0.58-1.74 ukat/L; Bilirubin: 5.0-21.0 umol/L; GGT 0.15 -0.65 ukat/L)

Study Day	C-Reactive Protein (CRP) (normal range 0.0 – 5.0 mg/L)	IgE- celkove (normal range 0-240 ng/mL)	CMV – IgG (reference – negative)	CMV- IgM (reference – negative)	Iron (normal range 9.0 – 26.0)
*26	11.2	-	-	-	-
*27	-	312	-	-	-
**41	-	-	positive	negative	6.8

*Hospital laboratory results dated (b) (6) ** Hospital laboratory results dated (b) (6)

The urticaria responded to intramuscular bisulepin, a highly selective H₁ antihistamine. On Day 28, the skin lesions had begun to regress. The patient did not take study drug on Day 27, but did receive study drug on Days 28 and 29 without return of urticaria. On Day 33 the study drug was discontinued by the investigator. The Hypersensitivity Expert Committee review assessed this definite hypersensitivity reaction (urticaria) as possibly related to study drug.

Reviewer's Comment: This definite hypersensitivity reaction (urticaria) is possibly related to mirabegron. However, an inadvertent re-challenge did not result in recurrent symptoms.

Subject 3105-2977: Gastric Ulcer: The subject is a 69 year old white Slovakian male randomized to mirabegron 50 mg on (b) (6). The subject received a total of 113 days of study drug. The study treatment was not discontinued due to the adverse event. On day 79, a serious adverse event of gastric ulcer was reported. The subject had a relevant medical history of ischemic heart disease and was on chronic acetylsalicylic acid (50 mg) therapy for 2647 days. On an unknown day in (b) (6), the subject developed gastric pain and on day 79, the subject was hospitalized for this gastric pain. During hospitalization, the subject had a gastroscopy and was diagnosed with a gastric ulcer. Study drug was interrupted from day 79 to day 86 due to this serious adverse event. The subject was given omeprazole orally for a total daily dose of 40 mg for the indication of gastric ulcer. On day 86, the subject was discharged from the hospital and the serious adverse event of gastric ulcer was reported as resolved.

Reviewer's Comment: Chronic acetylsalicylic acid therapy confounds attribution to mirabegron.

Subject 3105-2977: Atrial Fibrillation: Ischemic Heart Disease Decompensation: The subject is a 76 year old white Slovakian male randomized to mirabegron 50 mg on (b) (6). The subject received a total of 224 days of study drug. The study treatment was not discontinued due to the adverse event. The subject withdrew consent on day 224. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg. A narrative was written for this subject due to the event atrial fibrillation. The medical history included left inguinal herniotomy (1974), ischemic heart disease (since 1975), atrial fibrillation (since 1992), hypertension (since 1992), benign prostatic enlargement (since 1999-02), hypercholesterolemia (since 2007-04-17), senile cataract (since 2008-01-03), myopia (since 2008-01-03), gonarthrosis (arthritis of the knee) (since 2008-04-29). Concomitant medications on Day 182 when the adverse event of atrial fibrillation was reported were: verapamil, warfarin, digoxin, atorvastatin, tamsulosin, desmopressin and isosorbide.

On day 182, adverse events of atrial fibrillation and right bundle branch block were reported. The subject had a relevant medical history of atrial fibrillation (since 1992) and prior to study entry the subject was receiving verapamil orally for a total daily dose of 240 mg and warfarin orally for a total daily dose of 3 mg for the indication of atrial fibrillation. The screening physical examination (day -22) documented atrial fibrillation and the screening ECG was interpreted as abnormal with findings of atrial fibrillation and right bundle branch block. On day 97, the subject had a change in cardiovascular medication for the indication of atrial fibrillation; the subject's digoxin was reduced to a total daily dose of 0.125 mg, verapamil was increased to a total daily dose of 360 mg, and warfarin was increased to a total daily dose of 4.5 mg. On day 97, the dose of isosorbide was also reduced to a total daily dose of 20 mg for the indication of hypertension. On day 182, the subject's ECG findings showed atrial fibrillation and a right bundle branch block. On day 250, the adverse event of atrial fibrillation was reported as resolved and on day 278, the adverse event of right bundle branch block was reported as resolved.

On day 238, adverse events of cholelithiasis and hyperuricemia were also reported. The subject was given urodeoxycholic acid orally for a total daily dose of 500 mg for the indication of cholelithiasis.

On day 251 (patient withdrew consent on Day 224), serious adverse events of atrial fibrillation and ischemic heart disease were reported and the subject was admitted to the hospital. At the time of admission, the subject presented with dyspnea, an irregular heart beat, heart rate of 90 bpm, blood pressure of 150/90 mmHg and edema of the lower extremities that was worse on the left side (hospital discharge summary (b) (6)). ECG at hospitalization showed atrial fibrillation, heart rate of 94 to 120 bpm, complete RBBB, QRS 0.12, biphasic T in V4-V6. There were no new ischemic changes. Subsequent ECGs showed atrial fibrillation and complete RBBB. During hospitalization, the subject's condition improved as evidenced by improvement of arrhythmia and cardiac decompensation (hospital discharge summary (b) (6)). Due to chronic renal failure and repeated episodes of hypotension during hospitalization, ACE inhibitors were removed from the therapeutic regimen. On day 268, cardiovascular medication changes were again made for the indication of atrial fibrillation: verapamil and warfarin were reduced to 160 mg and 2.5 mg respectively. On day 268, the subject was discharged from the hospital and the serious adverse events of atrial fibrillation and ischemic heart disease were reported as resolved. The end of treatment physical examination (day 278) showed edema in lower extremities and symptoms of atrial fibrillation.

The tables below are from the patient narrative:

Table 2: Vital Sign Averages

Visit/ Device	Blood Pressure (mmHg)	Heart Rate (beats/ minute)
Baseline: Home Device	175/81	65
Baseline: Office Device	170/80	64
Month 1: Home Device	135/80	69
Month 1: Office Device	138/80	62
Month 3: Home Device	143/93	65
Month 3: Office Device	145/90	63
Month 6: Home Device	161/91	64
Month 6: Office Device	155/90	64

Table 3: Study Related ECG Findings

Study day	HR Mean (bpm)	PR Mean (ms)	QRS Duration (ms)	RR Mean (ms)	QTCF Mean (ms)	QTCB Mean (ms)	QT Mean (ms)	ECG Interpretation	Comments
-22	68	-	139	887	420	431	400	abnormal	atrial fibrillation; right bundle branch block; ST segment depressed; T-wave flattening or inversion in two or more leads
182	118	-	134	510	431	484	343	abnormal	atrial fibrillation; right bundle branch block; T-wave flattening or inversion in two or more leads
278	107	-	146	560	442	498	349	abnormal	atrial fibrillation; right bundle branch block; ST segment depressed; T-wave flattening or inversion in two or more leads

Table 4: Relevant Laboratory Results

Study Day	Blood Urea Nitrogen (normal 2.50 – 7.50 umol/L)	Creatinine (normal 0 – 103.428 umol/L)	Urate (normal 208.16 – 416.36)	Bilirubin (normal 0 – 18.64 umol/L)
-22	6.07	106.1	410.41	33
28	7.50	115.8	416.36	24.8
182	7.85	106.1	398.52	31
278	16.42	201.6	481.79	40.2

Reviewer's Comment: This is a complex case. The patient has a past history of atrial fibrillation, hypertension and ischemic heart disease for which he was taking verapamil, digitalis, warfarin and isosorbide. Atrial fibrillation was present on the screening ECG. On Day 97, the patient's digoxin dose was reduced and atrial fibrillation was reported subsequently. The cardiac decompensation occurred 27 days after the study drug was discontinued. I agree with Sponsor that the association with these events and mirabegron is unlikely.

Subject 3117-3170: Cerebrovascular Accident: The patient is a 64 year old white Polish male randomized to mirabegron 50 mg on (b) (6). The subject received a total of 364 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment. The medical history included probable previous myocardial infarction (before by-pass surgery in

2004) as diagnosed by a cardiologist (since 2004), stroke (1993 and 1998), arterial hypertension (since 1994), obesity (since 1994), penile curvature (1994 through 1994-10-26), surgical correction of penile curvature (1994-10-26), adult-onset diabetes (since 2000), coronary artery disease (2000 through 2004), internal carotid artery stenosis (2001 through 2001-02-07), surgical treatment of internal carotid artery stenosis (2001-02-07), bronchial asthma (since 2004), by-pass surgery (CABG) (2004), depression (since 2004), hypercholesterolemia (since 2006-01), benign prostatic hyperplasia (since 2006-06). The concomitant medications the subject was taking at the time of the event (Day 61) were: acetylsalicylic acid, mianserin (depression), theophylline, tianeptine (depression), bisoprolol, furosemide, ramipril, spironolactone, tamsulosin, lacidipine and simvastatin.

On day 61, a serious adverse event of cerebral apoplexy (stroke) was reported. The subject was noted to have dysphonia and was hospitalized for the serious adverse event of cerebral apoplexy. On day 72, the subject was discharged from the hospital and the serious adverse event of cerebral apoplexy was reported as resolved.

Reviewer's Comment: This diabetic patient has prior history of carotid artery stenosis, carotid artery surgery, two strokes, a myocardial infarction, and coronary artery bypass surgery. In this patient with multiple vascular risk factors and two previous CVAs, the attribution of causality to mirabegron is confounded and unlikely.

Subject 3120-2849: Sick Sinus Syndrome: The subject is a 77 year old white Polish female randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The subject received a total of 365 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg. The medical history included arterial hypertension (since 1980), myocardial ischemia (since 1980), hyperthyroidism (since 1992), type 2 diabetes mellitus (since 2003), hypercholesterolemia (since 2009), and overactive bladder (since 2007-04-12). Concomitant medications subject received at the time of the event were: metoprolol, indapamide, trimetazidine, losartan, thiamazole, gliclazide, theophylline and molsidomine. During the screening period, this subject had an adverse event of sinus arrhythmia from day-12 to day -3.

On day 22, the subject was hospitalized for arterial hypertension and incidents of MAS (Morgagni-Adams Stokes) incomplete. The ECG on hospitalization admission showed atrial fibrillation with a ventricular rate of 70 – 90 beats per minute (bpm) with a normal heart axis. There was ST segment depression in leads I, II, III, aVF, and V2-V6. ECGs during hospital stay (unspecified date) showed atrial fibrillation with a substitute AV nodal rhythm of 40 beats per minute with a normal heart axis. This ECG showed ST segment depression in leads I and II. A 24-hour monitoring ECG showed atrial fibrillation during the entire 24-hour period with a ventricular rate of 55-133 bpm during the day and a rate of 50-100 bpm during the night. The average ventricular rate was 68 bpm with ventricular extrasystoles of 30 per hour. No supraventricular extrasystoles Lown's I A class were detected. No AV conduction disturbances detected or ST segment changes detected. The subject was asymptomatic and had no complaints were reported. A coronary arteriogram on day 26 showed no significant flow obstruction with

positive presence of peripheral lesions in the left coronary artery and its circumflex and anterior descending branches and the right coronary artery; 90% ostial narrowing was detected in the first diagonal branch. An echocardiography on day 25 showed a normal left ventricular systolic function with “mitral valve –cuspidal” thickening and grade 1 mitral regurgitation with left atrial enlargement and an ejection fraction of 65 %. There were no changes made to study drug due to these events. During hospitalization, on day 29, the subject received an implantation of a cardio-stimulatory electrode device (pacemaker). On day 25, the adverse event of arterial hypertension was reported as resolved and on day 29, the serious adverse event of sick sinus syndrome was reported as resolved.

On day 126, a serious adverse event of implanted cardiostimulator not working correctly was reported. On day 126, the subject was hospitalized for aberrancy of stimulation of atrial electrode of pacemaker. On day 130, atrial electrode reposition of pacemaker was performed.

Reviewer’s Comment: This patient had a history of myocardial ischemia, hypertension, and hyperthyroidism. The screening ECG showed sinus arrhythmia. The Sponsor observes that propafenone (Days -12 to -10) might have been used for a baseline tachyarrhythmia. Beta blockers, methimazole, and theophylline may have also contributed to the effects seen. There is sufficient evidence that a large component of the events seen may have been present at baseline and possibly exacerbated by medications. The cardiovascular adjudication committee did not find evidence of ischemia associated with this event. I cannot attribute these events to mirabegron.

Subject 3140-1831: Humerus Fracture: Concussion: The subject is a 65 year old white Hungarian male randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The subject received a total of 358 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4. The medical history included wrist fracture on the right side (1992), hypertension (since 2002), fracture of the left third metatarsal (2004), prostatic hypertrophy (since 2005), osteopenia (since 2005-08), hypacusia of the right ear (since 2007-04) and cerebral atherosclerosis (since 2008-03). Concomitant medications (to Day 148): metoprolol.

On day 148, a serious adverse event of right-sided humerus fracture with dislocation was reported and the subject was hospitalized for a right-sided humerus fracture with dislocation and had exploratory surgery on day 149. The subject had a relevant medical history of previous fractures of the right wrist and left third metatarsal. An adverse event of right-sided humeral fracture was reported from day 142 to day 147 and the subject was reportedly under the influence of alcohol at the time of this event. Study drug was interrupted for 9 days (dates not provided). The event was reported as resolved on day 190.

On day 299, a serious adverse event of concussion of the brain was reported and the subject was hospitalized for a moderate concussion of the brain. The subject was reportedly intoxicated with alcohol and was involved as a pedestrian in a motor vehicle accident. Unspecified surgery was used to treat this serious adverse event. Study drug was interrupted for 10 days due to the event

(dates not provided). Additional adverse events associated with this serious adverse event of concussion of the brain were wound of the face (day 299 to day 31), fracture of the nasal bone (day 299 to day 317), deflection of the septum (day 317 and ongoing) and fracture of the fourth rib left side (day 299 to day 324) were reported. The event of concussion of the brain was reported as resolved on day 302.

On day 28, an adverse event of elevated GGT laboratory level (160 U/L) was reported. The subject had a relevant medical history of hypertension. No changes were made to study drug due to this event. The subject's GGT was elevated at 91 U/L during the screening period (day -15) and was 160 U/L on day 28. On day 168, the event of elevated GGT was reported as resolved. Other liver chemistries were spuriously elevated including an increased level of AST on day 28 and increased level of alkaline phosphatase on day 168.

Study Day	Alanine Aminotransferase (ALT) (normal range 1 - 39 U/L)	Aspartate Aminotransferase (AST) (normal range 1 - 39 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 18.64 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 10 - 49 U/L)	Eosinophils (normal range 0-480 10 ⁶ /L)
-15	20	30	75	4.6	91	380
28	31	59	79	5	160	530
168	17	28	230	3.1	43	340
358	20	27	94	2.4	50	110

Source: Patient narrative

Reviewer's Comment: The patient has a history of osteopenia and has suffered previous wrist and foot fractures. The patient was reportedly under the influence of alcohol at the time of his humerus fracture as well as at the time of his being a pedestrian involved in a motor vehicle accident and suffering a concussion of the brain. Both injuries are apparently related to alcohol abuse and not to obtundation secondary to the study drug. The alkaline phosphatase can be related to healing fracture. The other elevations of liver enzymes can be attributed to alcohol abuse. It is unlikely mirabegron is related to any of these events.

Subject 3304-0619: Cellulitis: The subject is a 75 year old white British male randomized to mirabegron 50 mg (b) (6). The subject received a total of 358 days of study drug. The study treatment was not discontinued due to the adverse event. The medical history reveals no other listed conditions other than overactive bladder (since 1989). There are no concomitant medications.

The subject had no relevant medical history and no changes were made to the study drug due to this event. On day 91, the subject experienced leg pain and visited the emergency department. The subject was hospitalized overnight with cellulitis and was discharged on day 92. The subject was treated with oral erythromycin at an unknown dose for the indication of cellulitis left leg. On

day 94, the subject was readmitted to the hospital with increasing leg pain and decreased mobility and was treated with intravenous flucloxacillin at an unknown dose. On day 99, the subject was discharged and prescribed oral flucloxacillin for a total daily dose of 2 grams and oral amoxicillin for a total daily dose of 1500 mg. On day 147, the event was reported as resolved. The patient's baseline white blood cell counts were in the normal range at baseline. There were no CBC data in report at the time and during the acute event. On Day 183, the neutrophil count was $1960 \times 10^6/L$ (NI range 2110-6900). On Days 21 and 358 the neutrophil counts were 3490 and 2110 respectively.

Reviewer's Comment: The patient had no confounding factors, history of trauma, medications, or indication of immunological compromise. While this case of cellulitis arose in association with mirabegron use by itself it is difficult to conclude a causal association.

Subject 3433-1273: Atrial Flutter: The subject is an 85 year old white Latvian female randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The subject received a total of 359 days of study drug. The study treatment was discontinued due to the adverse event of atrial flutter on day 359 ([REDACTED]^{(b) (6)}). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg. The medical history included right wrist trauma (1989), arterial hypertension (since 1993), hypothyroidism (since 2003), goiter (2004-04-02 through 2005-09-09), bilateral gonarthrosis (arthritis of the knees) (since 2005), coxarthrosis, sin (left-sided hip arthritis) (since 2006-05-31). Her concomitant medications on Day 359 were: bisoprolol, enalapril, levothyroxine, acetylsalicylic acid, vinpocetine (hypertension), felodipine and pancreatin (prescribed for the adverse of stomachache (duration of AE Days 243-248).

On day 359, a serious adverse event of atrial flutter was reported. Relevant medical history included arterial hypertension since 1993 and hypothyroidism since 2003. The subject presented to the hospital on day 359 because of self-monitored low blood pressure. The subject had no other symptoms or complaints upon admission. An ECG performed upon hospitalization revealed atrial flutter with a heart rate of 134 bpm, QRS of 0.09 s, a QT interval of 0.031 s, and left ventricular hypertrophy. A repeat ECG on day 360 showed a heart rate of 108 bpm. ECG results at baseline and day 182 indicated a first degree AV block and day 371 indicated atrial fibrillation. Concomitant treatment for atrial flutter are reported in Table 1. On day 362, blood parathyroid hormone level was 11.1 pmol/l, TSH was 6.31 mIU/mL (increased), FT4 was 1.23 ng/dL (low), and FT3 was 1.84 pg/mL (in normal range). An echocardiogram was done during hospitalization; however, the results are unavailable. Creatinine kinase-MB and troponin levels were within normal limits. The study treatment was discontinued due to the adverse event of atrial flutter on day 359. She was treated for atrial fibrillation, coronary artery disease and chronic heart failure. In the Sponsor's opinion, her hypothyroidism was well controlled. The event was reported as resolved with sequelae on day 363 when the subject was discharged from the hospital.

Reviewer's Comment: This event should be classified as atrial fibrillation. Even considering the patient's ongoing medical conditions, this event occurred while

the patient was receiving study drug and a causal association with mirabegron cannot be ruled out.

The Sponsor does not plan to market mirabegron 100 mg. Narratives for the 100 mg mirabegron arm are presented where a causal association cannot be ruled out or where there is an absence of confounding factors.

Subject 1630-6655: Liver Function Test Abnormal: The subject is a 58 year old white American female randomized to mirabegron 100 mg on (b)(6). The subject received a total of 39 days of study drug. The study treatment was discontinued due to the adverse event of elevated liver function on day 39 (b)(6). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg. The medical history included allergy to cats (since 1954), pneumonia (1955), Bell's Palsy(1966 and 1992), excision of fibroids (1980), Hashimoto's thyroiditis (since 1980), sinus surgery to excise polyp (1981), arthritis (since 1987), left hip bone graft to thumb (1989), traumatic amputation of left thumb with reconstruction (1989), kidney stone (1995), allergy to sulfa (since 1997), presbyopia (since 1998), lumbar/sacral radiculopathy (since 2001), L 4-5 discectomy (2001-08), hot flashes (2003), myopia (since 2003), laser surgery for left leg varicose veins (2004), menopause (since 2004-07), asthmatic bronchitis (2007-12), bronchial asthma (since 2007-12), hyperlipidemia (since 2008-05-12), right middle finger injury (since 2008-06-18), small cystocele (since 2008-11-04). Concomitant medications include: levothyroxine, ibuprofen, fish oil, multivitamins, and salbutamol inhaler.

On day 29, the serious adverse event of elevated liver function was reported. The subject had a relevant history of hyperlipidemia and had slightly elevated liver function tests prior to the start of the 047 study, which were determined to be not clinically significant in that study. Baseline laboratory results for the 047 study were ALT 52 IU/L (1- 30 U/L), AST 51 IU/L (range 1-32 U/L), ALKP 90 IU/L (range 31-121 U/L), and total bilirubin 0.30 mg/dl (range < 0-18.64 umol/L or 0.1-0.3 mg/dL). The subject reported drinking only a few glasses of wine per month. The subject was asymptomatic and pertinent negatives included no icterus, jaundice, nausea, vomiting or abdominal tenderness. Study drug treatment was discontinued on day 39 due to the adverse event of elevate liver function. The subject was seen on day 59, by the investigator for follow up laboratory results and was withdrawn from the study due to elevated liver function.

Laboratory Results from Study Visits

Study and Day	ALT (Normal 1-30 U/L)	AST (Normal 1-32 U/L)	ALKP (Normal 31-121 U/L)	Total Bilirubin (Normal 0-18.369 umol/L)	GGT (Normal 6-32 U/L)	Eosinophils (Normal 0-480 10 ⁶ /L or 0-0.007 fraction)
178-CL-047 (50mg) Day 1= July 1, 2008						
Day-20	52	51	90	5.1	23	660
Day 1	72	60	112	6.3	34	740
Day 30	82	60	108	6.8	40	490

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Day 57	58	52	109	5.1	36	340
Day 86	75	64	108	4.8	33	580
178-CL-049 (100mg) Day1= November 18, 2008 Received 39 day of Study Drug						
Day -14	57	55	96	4.4	27	0.066
Day 29	145	110	109	4.8	32	0.077
Day 36	217	167	121	8.7	44	NR (Not reported)
Day 57	448	286	332	5.5	146	0.076
Day 80	243	181	391	8.7	166	0.195
Day 386	46	44	116	4.4	26	NR

Source: Patient narrative and CRF for patient Study 178-CL-047

The subject was seen by her primary care physician (PCP) on day 50. Laboratory results confirmed the subject was hepatitis B and hepatitis C negative. Abdominal ultrasound was performed on day 51 and reported the liver as normal with no focal mass. There was no evidence of intra or extrahepatic biliary duct dilation. The common bile duct measured 0.43 cm. The gallbladder contained multiple non-mobile non-shadowing foci most likely consistent with small gallbladder polyps. Laboratory examinations results were obtained on further follow up with the subject's PCP. Lab results from day 50 were reported as follows; HBsAg non-reactive, HCV Ab non-reactive, ALT 462, AST 299, ALKP 208, total bilirubin 0.4 and eosinophils (day 66) 8.2% (normal range 0-5%) with other laboratory ranges not provided. The PTT was within normal limits (9.9 sec; range 9.4-11.4) and INR was 1.0 (day 73).

On day 66, the subject consulted a hepatologist to test for causes of the elevated LFT's. Results of serology are reported in table below. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting, abdominal tenderness, fever, chills, anorexia, fatigue, weakness, weight loss, gas/bloating, rashes, new joint pain or malaise. The subject did report pruritus of the arms and legs for 6 months, night sweats (that preceded the use of study drug in the 047 and 049 studies) and arm pit itch for 2 weeks prior to the hepatologist visit of day 66. Physical examination findings were normal except for tenderness of the left lower ribs. No organomegaly was detected either by palpation or percussion.

Hepatology Lab Tests Day 66: Patient 1630-6409

Study Day	HBsAg	HBc Ab	HAV IgM	HCV Ab	ANA	SMA (normal range < 1:40)	AMA (normal range 0.0 – 0.3)	A1AT (normal range 100 – 190 mg/dl)	ferritin (normal range 30 – 400 ng/ml)	iron saturation
66	negative	negative	negative	negative	initially negative repeat +1:80	negative	negative (<0.1)	178	329	29%

Source: Patient Narrative Table 4

Liver biopsy performed on day 77 revealed dense lymphocytic infiltrate and granulomas in the portal tracts with focal destruction of bile ducts, abundant plasma cells and rare mixed eosinophils. Granulomas were also present in the lobules with marked piecemeal necrosis and lobular inflammation; acidophil bodies were noted and stainable iron was present (1+/4+). No steatosis was seen and focal portal fibrosis was identified on trichrome stain. In a subject with negative viral serology and negative serum antibodies, the differential diagnoses that were considered included autoimmune hepatitis, primary biliary cirrhosis overlap syndrome and drug reaction. The overall impression by the hepatologist was that due to the temporal association of the elevation in liver function tests and the descriptive features of the biopsy, taken together, the picture was considered more consistent with drug induced liver injury and less consistent with autoimmune hepatitis. It was suspected the incident would resolve without further treatment. On day 141, at the time the liver enzymes returned to within normal limits, this adverse event of elevated liver enzymes was reported as resolved.

Reviewer's Comment: The patient had baseline elevated serum AST, serum ALT and serum alkaline phosphatase, as well as baseline eosinophilia. On Day 50 of Study 049, the serum AST, ALT and alkaline phosphatase was markedly increased. Based on the liver biopsy results, drug induced liver injury is a definite consideration. The use of ibuprofen and the patient's autoimmune history are confounding factors. Outside lab values on Day 141, were ALT 39, AST 42, Alk Phosph 115 and Total bilirubin 0.3. These were compatible with pre-drug levels.

Subject 1630-7319: Hypertension: The subject is a 77 year old white US male randomized to mirabegron 100 mg on [REDACTED]^{(b) (6)}. The subject received a total of 372 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg. The medical history included Grade 2/6 systolic murmur (since 1933), rheumatic fever (1933), nephritis (1946), atrophic left testis (since 1948), head injury (1951), excision of pilonidal cyst (1956), myopia (since 1970), presbyopia (since 1970), hypertension (since 1973), Paget's disease (asymptomatic since 1975), kidney stones (1998), bilateral onychogryphosis great toenails (since 1998), intermittent insomnia (since 1999), right inguinal hernia repair (1999), BPH (since 2000), hyperlipidemia (since 2001), bilateral carpal tunnel syndrome (since 2002), occasional headaches (since 2002), gastritis (2003-10 through 2003-11), intermittent anemia (since 2004), anxiety (2006), monoclonal gammopathy of undetermined significance (since 2006), non-insulin dependent diabetes mellitus (since 2008-02), benign scalp lesion removal (2008-05), occasional chest pain of unknown origin (since 2009-01-06). On the day of onset (Day 251), the patient was on the following medications: allopurinol, lisinopril, metoprolol, terazosin, simvastatin, acetylsalicylic acid, multivitamins, and acetaminophen.

On Day 251, the serious adverse event of worsening hypertension was reported. The subject had a relevant medical history of Grade 2/6 systolic murmur, hypertension, occasional chest pain of unknown origin (echocardiogram and nuclear stress test unremarkable), anxiety, BPH, nephritis and hypercholesterolemia. On Day 244, the adverse event of hypertension was reported and the subject's metoprolol was increased from 50 mg twice daily to 100 mg twice daily. The subject

reported he had been under a lot of stress due to his wife’s hospitalization for a broken leg, was not feeling well and drove himself to the hospital on day 251. Study drug treatment was interrupted beginning on day 251.

The subject was admitted to the hospital on day 251 with an elevated blood pressure of 248/120 mmHg associated with a headache. In the emergency room, the subject was treated with acetaminophen and glyceryl trinitrate. The subject reported having had a bee sting to his right upper lip (day 250) and although he had localized pain, there was no edema, wheezing, shortness of breath or urticaria. Later in the evening, the subject reported the onset of a headache and facial warmth which was typical when his blood pressure is high. When the subject checked his blood pressure, systolic was reported at 200 mmHg and he felt anxious, but otherwise had no chest pain, shortness of breath or neurologic symptoms. The subject reported intermittent headaches for the past few months (day 5 to day 122), usually affecting the front and sides of the head and were self-limiting. There were no reported symptoms of chills, fever, sweats, cough, sputum production, rash, joint aches, nausea, vomiting, abdominal pain, diarrhea or dysuria. Notable physical examination findings were a murmur in the left carotid artery, systolic murmur and trace edema in the lower extremities. ECG was normal with normal axis and intervals, no Q-waves and no ST-T changes, head CT showed no intracranial process, chest X-ray showed no acute infiltrate or congestion change. The subject’s blood pressure came under control later in the day with readings ranging from 137-180 /70 - 80 mmHg with the addition of amlodipine 10 mg orally. Myocardial infarction was ruled out and arrhythmias were noted on telemetry (specifics not available in hospital records). On day 252, the subject was discharged and adverse event of worsening hypertension was reported as resolved. The subject was instructed to follow up with his primary care physician to discuss whether he should resume study drug. Study drug treatment was resumed on day 258.

Patient 1630-7319 Average Vital Signs

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	117/60	67
Baseline: Office Device	109/50	69
Month 1: Home Device	133/62	63
Month 1: Office Device	129/52	68
Month 3: Home Device	123/65	75
Month 3: Office Device	126/59	69
Month 6: Home Device	135/70	69
Month 6: Office Device	108/49	69
Month 9: Home Device	107/59	59
Month 9: Office Device	112/51	58
Month 12: Home Device	117/60	65
Month 12: Office Device	104/45	62

Source: Table 2 Patient narrative

Reviewer’s Comment: The patient was hypertensive, taking three anti-hypertensive medications at baseline. Around the time of the event, the patient had significant life stress related to his wife’s broken leg and hospitalization. His

blood pressure on Day 244 was increased from baseline, and on Day 258, it was observed to be 248/120 mm Hg. It is notable that on the previous day, the patient had suffered a bee sting to the upper lip. Although the patient appears to have had a negative rechallenge, he was on an additional antihypertensive medication, amlodipine. It is also noted that on Day 244 his dose of metoprolol was increased. There are confounding conditions and factors (stress), this worsening of hypertension did occur in association with mirabegron and a causal association cannot be excluded.

Subject 1667-6102: Acute Pancreatitis: Cholelithiasis: Renal Cysts: The subject is a 79 year old US female of Asian descent randomized to 100 mg of mirabegron on [REDACTED] (b) (6). This subject previously participated in the 178-CL-047 study and was randomized to the placebo treatment. The subject received a total of 77 days of study drug. The study treatment was discontinued due to the adverse events of acute pancreatitis, cholelithiasis, multiple bilateral renal cysts, allergy to erythromycin, gastroenteritis and herpes zoster of the right upper quadrant on Day 77. The medical history included error of refraction (since 1978), menopause (since 1980), osteoporosis (since 2000), arthritis (since 2007), arteriosclerotic cardiovascular disease (since 2007-01-11), back lipoma (since 2007-01-22), asthma (since 2007-02), urinary tract infection (2007-08 through 2007-09), hypothyroidism (since 2007-09-18), dyslipidemia (since 2007-11), eczema (2007-11 through 2008-02), dense bilateral cataract (since 2008-01-22). Concomitant medications on Day 77 include: acetylsalicylic acid, rosuvastatin, montelukast, ibuprofen, and fluticasone nasal.

On Day 30, an adverse event of increased GGT was reported. The subject had no relevant medical history. No changes were made to study drug due to this event. No concomitant medications were noted due to this event. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. Eosinophils remained within normal limits throughout the study. The subject's GGT was elevated at screening (Day -13) and throughout the study. On Day 29, the subject's GGT increased to greater than twelve times the upper limit of normal associated with mild elevations of ALT, AST and ALKP. GGT level decreased and was almost within normal limits by day 142; ALT, AST and ALKP normalized by day 142. On day 145, the adverse event of increased GGT was reported as resolved.

On Day 79, serious adverse events of acute pancreatitis, cholelithiasis and multiple bilateral renal cysts were reported. The subject had no relevant medical history. On Day 78, the subject experienced severe abdominal pain beginning one day prior and was admitted to the hospital. The subject reported not being able to take study medication due to the hospitalization. The last dose of study drug was administered on Day 77. No concomitant medications were noted due to these events. On Day 79, an abdominal ultrasound was performed revealing a 6 mm non-obstructive stone on the top of renal bilateral cysts with no evidence of hydronephrosis. An X-ray on an unknown date in 2009-01 showed gallbladder stones. An abdominal and pelvic computed tomography (CT) scan showed multiple small calcifications in the gallbladder (likely cholelithiasis) and bilateral renal cysts. On Day 79, the subject's reported amylase was 141 U/L (normal range 30-110 U/L) and lipase was 756 (normal range 23-300 U/L). An endoscopic retrograde cholangiopancreatography (ERCP) done on Day 84 showed evidence of normal

pancreatic duct with no filling defect and interruption. The common bile duct size was normal with no intrahepatic duct dilatation, no filling defects. The gallbladder looked normal, the cystic duct was open and the papilla was normal. There was good bile drainage. The subject was diagnosed with cholelithiasis, multiple bilateral renal cysts and acute pancreatitis. On Day 86, the subject's lipase was 12000 U/L with an amylase of 1300 U/L. On Day 88, the subject's amylase had normalized. On the following day, Day 89, the subject was afebrile, feeling well, and was discharged from the hospital. Upon discharge on Day 89, the serious adverse events of cholelithiasis and multiple bilateral renal cysts were reported as recovering while the serious adverse event of acute pancreatitis was reported as resolved.

On day 79, an adverse event of allergy to erythromycin was also reported. The time period of treatment with erythromycin was not reported. There was no further description of this allergic reaction. On day 87, adverse events of gastroenteritis and right upper quadrant herpes zoster were reported. The subject was treated with oral pantoprazole 40 mg daily (day 87 through day 89) for the indication of gastroenteritis as well as oral acyclovir 4 g daily (day 87 through day 89) for the indication of right upper quadrant herpes zoster. No additional symptoms or clinically significant findings were reported due to these events. The adverse events of gastroenteritis and right upper quadrant herpes zoster were reported as resolved on day 89 (hospitalization discharge day).

Reviewer's Comment: It appears that this patient with cholelithiasis suffered an episode of gallstone-related pancreatitis.

Subject 2037-0238: Thoracic Vertebral Fracture: The subject is a 60 year old white US female randomized to mirabegron 100 mg (b) (6). The subject received a total of 59 days of study drug. The study treatment was discontinued on Day 59 due to the adverse event of back fracture (T12) (spinal fracture) on day 57. The medical history included allergy to penicillin (since 1958), allergy to sulfa (since 1958), gallbladder removed (1998), menopause (since 2002), hiatal hernia (since 2008-07), acid reflux (since 2008-08). The patient was not taking any medication at the time of the event. The subject sustained a back fracture (T12-spinal fracture) and chest pain after she fell down the stairs of her home. In the hospital, A CT scan of the thoracic and lumbosacral spine revealed an acute fracture to the T12 vertebral body. A chest and lumbosacral spine x-ray showed no acute cardiopulmonary disease, no displaced fracture of the bony thorax and no acute abnormality of the lumbosacral spine. A cardiovascular evaluation was negative. The adverse event of "light-headed" was reported for this patient on Day 57 as were the events diaphoresis and nausea. There was no syncope, loss of consciousness or seizure activity reported around the time of the accident.

Reviewer's Comment: This 60 year old post-menopausal female suffered an acute T12 spinal fracture after falling down stairs.

2037-0516: Hemolytic Anemia: Thrombocytopenia: Liver Function Test Abnormal: The subject is a black 58 year old US female randomized to mirabegron 100 mg on (b) (6). The subject received a total of 183 days of study drug. The study treatment was discontinued due to the adverse events of charley horses/ leg cramps, hemolytic anemia, thrombocytopenia,

elevated liver function test and worsening elevated liver function test on Day 183. The medical history included anemia (since 1967), menopause (since 2003), osteoporosis (since 2004-02-02), high cholesterol (since 2005). Concomitant medications include ezetimibe/simvastatin, Vitamin D, red rice yeast dietary supplement and alendronic acid.

On day 182, the adverse events of hemolytic anemia, thrombocytopenia, and elevated liver function test were reported for this subject. Relevant medical history included family history of anemia and anemia (since 1967). Relevant concomitant medications included red rice yeast supplement (started 2009-08 to day 219). This supplement has been associated with hypersensitivity reactions (Allergy 1999: 54(12), 1330-1331). Baseline hemoglobin was 11.1g/L (just below the lower limit of normal), while platelets, hematocrit, leukocytes and erythrocytes were within normal range. Baseline liver function tests revealed slightly increased ALT, AST and GGT levels: 33 U/L, 37 U/L, and 48 U/L respectively. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting, bleeding episodes, rash, fever, or abdominal tenderness. Eosinophils, leukocytes and total bilirubin remained within normal limits throughout the study. The study drug was discontinued on Day 183.

On day 196, the event of worsening elevated liver function test was reported and was assessed as serious by the investigator. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness.

On day 219, the subject was evaluated by a hematologist. Symptoms included fatigue, weight loss, and pale conjunctivae. A peripheral blood smear showed red blood cell morphology of teardrops, poikilocytosis, anisocytosis, and hypochromia. Protein electrophoresis showed 0.9 g/dL monoclonal protein, glucose-6-phosphate dehydrogenase (G6PD) 18.1 (reference range 6-12 units not provided), haptoglobin <35, and light chain analysis showed free Lambda at 339, normal free Kappa and an abnormal ratio (units and reference range not provided). On day 226, the subject's blood work showed normal blood folate and vitamin B12, JAK-2 mutation analysis was negative, erythropoietin was markedly elevated at 521 (no reference range provided). The subject's Coombs tests were reported as negative on day 219 and day 246. On day 233, the subject's bone marrow biopsy showed a bone marrow clot with no spicules seen, hypercellular marrow with erythroid hyperplasia, area of relatively hypercellular marrow (focal), a relative decrease in megakaryocytes and iron stores were absent. On day 246, the subject's G6PD was 10.5 (reference range 6-12 units not provided), lactate dehydrogenase 378 (reference range 97-236 U/L), free hemoglobin <1.0), hemoglobin A of 97, hemoglobin A2 of 2.0, parvovirus B19 serology was negative, haptoglobin was <35 (reference ranges not provided), free plasma hemoglobin was 0.9 m/dL (reference range 0.0-4.9) and free urine qualitative hemoglobin was negative. The subject was treated with oral iron supplement for a total daily dose of 650 mg and oral folic acid for a total daily dose of 1 mg.

Hematology Values Patient 2037-0516

Clinical Review

{Insert Reviewer Name}

{Insert Application Type and Number}

{Insert Product Trade and Generic Name}

Study Day	Erythrocytes (normal range 3.68-5.09 10 ¹² /L)	Erythroblasts (normal range 0.0 - 0.0)	Hemoglobin (normal range 116-154 g/L)	Hematocrit (normal range 0.34-0.45 fraction)	Leukocytes (normal range 3.6-10 10 ⁹ /L)	Platelets (normal range 145-390 10 ⁹ /L)
-15	3.98	n/a	111	0.34	5.2	173
29	3.84	n/a	107	0.33	4.1	162
181	2.98	12.0	83	0.27	6.1	96
188	3.08	5.0	86	0.28	7.4	85
196	3.02	16.0	84	0.28	6.8	87
219	3.04	77	84	0.27	5.9	90
233	2.74	n/a	78	0.25	5.5	80
246	2.70	n/a	78	0.24	5.9	75
250	2.72	24.0	76	0.24	n/a	n/a
260	2.67	n/a	76	0.25	6.9	77
261	2.67	n/a	74	0.23	6.5	65
2010-01-14 **	2.60	n/a	7.3	23.4	4.8	50

* n/a = not available

**Hospital laboratory reference ranges for the following tests: Erythrocytes 4.20-5.40 x10⁶, Hemoglobin 12.0-18.0 G/UL. Hematocrit 15.0-43.0 %. Leukocytes 4.0-11.0 x10³. Platelets 140-400 x10³

Liver Chemistries Patient 2037-0516

Study Day	Alanine Amino transferase (ALT) (normal range 1 - 30 U/L)	Aspartate Amino transferase (AST) (normal range 1 - 32 U/L)	Alkaline Phosphatase (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 18.6 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 - 32 U/L)	Eosinophils (normal range 0-480 10 ⁶ /L)
-15	33	37	85	6.5	48	0
29	31	26	97	6.5	88	20
181	68	54	110	7	150	120
188	41	40	106	7.7	141	70
196	77	73	120	9.2	179	0
260	18	27	69	8.2	83	0

Source for Hematology and Liver Chemistries Tables 2 and 3 of Patient Narrative

A chest/abdominal/pelvic CT scan did not show signs of malignancy; specifically, the CT showed no abnormal lymphadenopathy, spleen was of normal size, septated cyst in left ovary and two pulmonary nodules measuring less than 4mm.

On day 260, the hematologist diagnosed hemolytic anemia which had worsened despite study drug discontinuation of over one month prior. The subject's differential diagnosis was drug induced hemolysis versus G6PD deficiency and hereditary spherocytosis. Hemoglobin electrophoresis performed on an unspecified date was normal, red blood cell fragility test was normal and ferritin was over 300 (no reference ranges or units provided). On an unspecified date, the subject developed an ovarian cyst and monoclonal gammopathy of undetermined

significance (MGUS) with a small amount of monoclonal IgG lambda and a small M spike. Elevated liver function tests were appeared to be recovering.

On day 289, hematology symptoms were unchanged, qualitative G6PD was 842 U/L and quantitative G6PD was 326 U/10x12, red blood cell D-dimer was negative and fibrinogen was 253 mg/dL.

Reviewer's Comment: This patient had a history of anemia since 1967. The subject's hemoglobin was below normal limits at baseline and began decreasing further on Day 29, then again on Day 181. Study drug was stopped after 183 days. At baseline, the subject's serum ALT, AST and alkaline phosphatase were above normal limits, and on Day 196, the subject's serum ALT, AST and alkaline phosphatase were mildly elevated. Although drug-induced hemolysis cannot be ruled out, it has not been definitively shown, and it is notable that the patient had baseline anemia and elevated LFTs.

Subject 3024-1869: Angle Closure Glaucoma: The subject is a 55 year old white German female randomized to 100 mg of mirabegron on (b) (6). The subject received a total of 316 days of study drug. The study treatment was discontinued due to the adverse event of acute glaucoma on day 316 (b) (6). The medical history included hysterectomy non malignant (1985), gastritis (since 1999), hypertension (since 2004), stress incontinence (since 2007-01-30). Concomitant medications included omeprazole, metoprolol, and olmesartan/hydrochlorothiazide.

On day 316, the subject developed a severe headache and right eye pain. The subject was taken to the emergency room and was diagnosed with acute angle closure glaucoma of the right eye with an intraocular pressure of 58 mmHg. The subject was treated with ophthalmic brimonidine one drop three times daily (day 316 through day 323) and ophthalmic pilocarpine one drop four times daily (day 316 through day 323). On day 317, ophthalmologic examination revealed intraocular pressure of 17 mmHg in both eyes; slit lamp examination revealed that eyelids, conjunctivae, cornea, iris, pupils, and posterior chamber were normal; anterior chamber was shallow. The subject underwent iridectomy of the right eye as treatment for acute angle closure glaucoma (day 322 through day 323). Subsequently, on day 344, the subject underwent prophylactic iridectomy of the left eye.

Reviewer's Comment: There is no prior glaucoma history. This appears to be acute narrow angle glaucoma without confounding factors after 316 days of mirabegron. The results of a dedicated intraocular pressure study demonstrated no effect of mirabegron on intraocular pressure.

Subject 3027-2525: Arrhythmia: The subject is a 69 year old white German female randomized to mirabegron 100 mg on (b) (6). The study treatment was discontinued due to the adverse event of rhythmic heart disturbance aggravated on day 76 (b) (6). This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group with the same assigned subject number. A narrative was written for this subject due to the event of atrial fibrillation. The medical history included hypertension (since 1980), hysterectomy (1986), rhythmic heart disturbance (atrial fibrillation, since 2007),

cystitis (2008-09-11 through 2008-09-25. Medications on Day 74 include acetylsalicylic acid, metoprolol and olmesartan. On Day 74, her atrial fibrillation was aggravated and on Day 77, she was hospitalized due to atrial fibrillation. Upon admission, the subject had dyspnea on exertion with palpitations and a blood pressure of 130/80 mmHg. The subject was diagnosed with paroxysmal atrial fibrillation. ECG on day 77 showed atrial fibrillation with ventricular frequency of 90/min, 5 to V6. The subject was treated with amiodarone orally at a total daily dose of 200 mg to control frequency. Minimal success was achieved after multiple attempts to electrically convert the subject to a normal sinus rhythm. On Day 92, the ECG showed a ventricular frequency of about 80/min. and a QT with about 420 ms and the attending physician discharged the subject. At discharge, the event was reported as ongoing.

Reviewer's Comment: This patient has pre-existing atrial fibrillation that was exacerbated while she was on both tolterodine and mirabegron. A causal association with mirabegron is confounded and unlikely.

Subject 3314-3008: Fracture of Humerus: Muscle Injury: The subject is a 72 year old white Irish female randomized to mirabegron 100 mg on (b) (6). She received a total of 364 days of study drug. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4. She was not on other medications at the time of the event. The medical history included allergy to penicillin (since 1974), left mastectomy (for breast cancer) (1991), right mastectomy (prophylactic) (1992), left eye cataract (2008-09-16 through 2008-11-14), right eye cataract (2008-09-16 through 2009-02-17), worsening of OAB symptoms (since 2008-10-08), dry eyes (since 2008-10-28), dry mouth (since 2008-10-28), elective cataract surgery to left eye (2008-11-14), elective cataract surgery to right eye (2009-02-17), and overactive bladder (since 2004).

The subject reported falling a week prior to admission (fell down stairs and sustained a fractured neck of humerus on day 206). On day 208, the subject was admitted to the hospital with sudden onset chest pain with associated shortness of breath. The pain was reported to be located in the central chest. Upon hospital admission, the subject denied baseline shortness of breath and associated diaphoresis and vomiting. Diagnostic evaluations ruled out cardiac etiology or a pulmonary embolism. Final diagnosis was a musculoskeletal injury. There is no detail concerning the patient's state of alertness or attention.

Reviewer's Comment: This 72 year old female fell down stairs and sustained a fractured humerus after 206 days of mirabegron. Two days later she presented with chest pain of non-cardiac origin. There is not enough information to attribute a causal relationship.

Subject 3342-0389: Coronary Artery Disease: The subject is a 58 year old white Portuguese female randomized to mirabegron 100 mg (b) (6). The subject received a total of 186 days of study drug. The study treatment was discontinued due to the adverse event of coronary deficiency - probably (probable coronary deficiency) on day 186 (b) (6). The medical history included gastritis (since 2000), anxiety (since 2005), herniated disc (since 2005), pain (since 2005), hypertension (since 2006). Concomitant medications include omeprazole, celecoxib, clorazepate, paracetamol/tramadol and olmesartan.

On day 182, a serious adverse event of probable coronary deficiency was reported. The subject had a relevant medical history of hypertension. The subject had a body mass index of 32.4 kg/m². On day 182, electrocardiogram (ECG) results revealed nonspecific T-wave changes. On the same day, results of a second ECG revealed ST segment depressed and T-wave flattening or inversion in 2 or more leads. These results represented a change from the screening ECG findings which revealed no clinically significant abnormalities. On day 182, prior to the ECG, blood pressure (BP) and heart rate (HR) were measured at different times (i.e., morning and afternoon); all BP and HR measures were normal. A follow-up ECG was performed after 6 months (b) (6), and was interpreted as abnormal but not clinically significant; the abnormalities observed were sinus bradycardia and nonspecific T-wave changes. The serious adverse event of probable coronary deficiency was reported as ongoing at study completion.

Reviewer's Comment: In the absence of stress ECG and or other more invasive studies and the lack of associated symptoms, I am not able to discern what the above ECG changes indicate from a clinical perspective.

Subject 3367-2053: Increased GTT: Increased Transaminases: The subject is a 56 year old white Spanish female randomized to mirabegron 100 mg 11 February 2009. The subject received a total of 363 days of study drug. The study treatment was not discontinued due to the adverse event. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg. The medical history included appendectomy (1966), hypertransaminasemia (since 1977), uterine curettage (1999), irritable bowel syndrome (since 2003), diabetes mellitus (since 2005), intestinal polypectomy (2005), surgery for “melanocytic” nevus surgery (2008-05-12), fibromyalgia (since 2009-01). Concomitant medications include: glibenclamide, metformin, etoricoxib, paroxetine and metformin/vildagliptin.

On day 177, a medically significant increase of GGT value was reported. Pertinent negatives included no reported icterus, jaundice, nausea, vomiting or abdominal tenderness. No treatment was given for this event and it was reported as ongoing at the time of the last study visit (day 363). On day 363, the adverse event of transaminase elevation was reported.

Study Day	Alanine Aminotransferase (ALT/SGPT) (normal range 1 - 30 U/L)	Aspartate Aminotransferase (AST/SGOT) (normal range 1 - 32 U/L)	Alkaline Phosphate (ALKP) (normal range 31 - 121 U/L)	Total Bilirubin (normal range 0 - 18.639 umol/L)	Gamma Glutamyl Transferase (GGT) (normal range 6 - 32 U/L)	Eosinophils (normal range 0 - 480 U/L)
-21	42	35	55	4.3	143	120
35	42	32	53	6.7	151	130
177	59	55	57	6.7	220	80
209	55	41	54	6.0	204	70
363	94	108	56	5.1	171	130

Source: Subject 3367-2053 patient narrative.

It is of note that the liver function testing for this subject on Day -18 (22 August 2008) of Study 178-CL-046 had results of: ALT 49, AST 50, GGT 162 and bilirubin 7.0. On Day 99 of Study 046 the values were ALT 42, AST 33, GGT 166 and bilirubin 7.0.

Reviewer's Comment: In this subject with evidence of abnormal LFTs at baseline, there was moderate worsening of GGT on Day 177 and mild-moderate increase in AST and ALT on Day 363.

Reviewer's Comment: In the 50 mg mirabegron group, there was one case of new on set atrial fibrillation, one case of atrial fibrillation in association with serious pneumonia and 2 cases of atrial fibrillation in patients with pre-existing atrial fibrillation. There were two cases of significant allergic reactions: one patient with urticaria, and one patient with pre-existing anemia and elevated LFTs in whom hemolytic anemia was reported in the 50 mg mirabegron group. There was one case of liver injury and one case of worsened LFTs in a 100 mg mirabegron subject after 6 months of mirabegron exposure. There was one instance of worsening hypertension in a 100 mg subject who had significant hypertension at baseline. Gastrointestinal disorders were more frequent in mirabegron subjects than in tolterodine subjects: however, many of the cases of upper gastrointestinal conditions were confounded.

Table 44: Treatment Emergent Events Resulting in Permanent Discontinuation Study 178-CL-049 that Occurred in any SOC and also Preferred Terms that Occurred in at Least 2 Patients in Any Treatment Group

MedDRA (v9.1) System Organ Class Preferred Term n (%)	Mirabegron		Tolterodine ER 4 n=812
	50 mg n=812	100 mg n=820	
Any Serious Adverse Event	48 (5.9%)	5 (6.1%)	46 (5.7%)
Gastrointestinal Disorders	14 (1.7%)	9 (1.1%)	11 (1.4%)
Constipation	7 (0.9%)	2 (0.2%)	0
Nausea	3 (0.4%)	2 (0.2%)	1 (0.1%)
Dry Mouth	3 (0.4%)	1 (0.1%)	4 (0.5%)
Abdominal Pain	1 (0.1%)	2 (0.2%)	0
Abdominal Pain Upper	1 (0.1%)	1 (0.1%)	3 (0.4%)
Gastritis	2 (0.2%)	0	1 (0.1%)
Nervous System Disorders	10 (1.2%)	8 (1.0%)	10 (1.2)
Headache	5 (0.6%)	4 (0.5%)	3 (0.4%)
Dizziness	4 (0.5%)	2 (0.2%)	0
General Disorders and Administrative Site Conditions	4 (0.5%)	5 (0.6%)	2 (0.2%)
Fatigue	1 (0.1%)	3 (0.4%)	1 (0.1%)
Pain	2 (0.2%)	0	0
Cardiac Disorders	4 (0.5%)	4 (0.5%)	7 (0.9%)

Palpitations	0	2 (0.2%)	0
Myocardial Infarction	1 (0.1%)	0	2 (0.2%)
Angina Pectoris	0	0	2 (0.2%)
Atrial Fibrillation	0	0	2 (0.2%)
Eye Disorders	5 (0.6%)	3 (0.4%)	3 (0.4%)
Vision Blurred	3 (0.4%)	1 (0.1%)	1 (0.1%)
Dry Eye	3 (0.4%)	0	1 (0.1%)
Infections and Infestations	6 (0.7%)	2 (0.2%)	3 (0.4%)
Urinary Tract Infection	3 (0.4%)	0	1 (0.1%)
Neoplasms Benign and Malignant	0	7 (0.9%)	1 (0.1%)
Lung Neoplasm Malignant	0	2 (0.1%)	0
Prostate Cancer	0	2 (0.1%)	0
Skin and Subcutaneous Tissue	2 (0.2%)	5 (0.6%)	1 (0.1%)
Pruritis	0	2 (0.2%)	0
Vascular Disorders	4 (0.5%)	3 (0.4%)	4 (0.5%)
Hypertension	4 (0.5%)	2 (0.2)	3 (0.4%)
Renal and Urinary Disorders	2 (0.2%)	4 (0.5%)	4 (0.5%)
Dysuria	0	2 (0.2%)	0
Investigations	1 (0.1%)	3 (0.4)	4 (0.5%)
Liver Function Test Abnormal	0	2 (0.2%)	0
Injury Poisoning and Procedural Complications	3 (0.4%)	2 (0.2%)	1 (0.1%)
Reproductive System and Breast Disorders	2 (0.2%)	2 (0.2%)	3 (0.4%)
Psychiatric Disorders	1 (0.1%)	2 (0.2%)	1 (0.1%)
Blood and Lymphatic System Disorders	0	2 (0.2)	1 (0.1%)
Ear and Labyrinth Disorders	0	2 (0.2%)	2 (0.2%)
Vertigo	0	2 (0.2%)	1 (0.1%)
Metabolism and Nutrition Disorders	2 (0.2%)	0	3 (0.4%)
Musculoskeletal and Connective Tissue Disorders	0	2 (0.2%)	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.2%)	0	2 (0.2%)
Hepatobiliary Disorders	0	1 (0.1%)	0
Immune System Disorders	1 (0.1%)	0	1 (0.1%)
Pregnancy, Puerperium and Perinatal Conditions	1 (0.1%)	0	0
Surgical and Medical Procedures	0	1 (0.1)	1 (0.1)

Source: Table 26, Study Report 178-CL-049, page 129

Reviewer's Comment: Discontinuations due to adverse events were reported at low incidences in this study. It is notable that constipation, nausea, headache, dizziness, blurred vision, dry eyes, and urinary tract infection, all reported in <1% of patients in any treatment group, were reported more frequently as reasons for discontinuation in the mirabegron 50 mg group compared to the tolerodine ER group.

Below are brief narratives of selected discontinuations due to adverse events not previously mentioned in either "Deaths" or "SAEs", or cases that concern adverse event of special interest:

Subject 1838-6396: Urinary Tract Infection: The subject is a 46 year old US female randomized to mirabegron 50 mg on 17 October 2008. The subject received a total of 138 days of study drug. The study treatment was discontinued due to the adverse event of urinary tract infection (UTI) on day 138 (2009-03-03). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg. The medical history included tonsillectomy (1969), seasonal allergies (since 1987), sinus and nasal surgery (1995), hypothyroidism (since 2003), osteoarthritis (since 2003), arterial thrombosis (2003-02), sling procedure (2005-03), asthma (since 2006-03), plantar fasciitis (since 2007-01), UTI x1 (2007-04), depression (2007-05 through 2007-10-01), esophageal dilation (2007-08), Schatzki's ring (2007-08), staph infection of the left wrist (2008-06-25 through 2008-07-29), sleep apnea (since 2008-08-16). The patient underwent a tapered course of oral prednisone from Day 22 to Day 54 for increase in asthma.

On Day 67, an adverse event of UTI was reported. Relevant medical history included a UTI in 2007-04. Treatment included ciprofloxacin orally at a daily dose of 1000 mg and sulfamethoxazole and trimethoprim orally at a daily dose of 800/160 mg. There was no change to the study treatment dose as a result of the adverse event. There were no other symptoms or complaints noted. The event was reported as resolved on day 92. On Day 121, a second adverse event of UTI was reported. Treatment included sulfamethoxazole and trimethoprim orally at a daily dose of 800/160 mg. No urine culture results were reported and there were no other symptoms or complaints noted. The study treatment was discontinued due to the adverse event of UTI on Day 138. The event was reported as resolved on Day 128.

Reviewer's Comment: The patient had a history of UTI. Two UTIs were reported in this study, one on Days 67 and one on Day 121.

Subject 2040-8126: Clavicle Fracture: The subject is a 56 year old white US female randomized to mirabegron 50 mg on [REDACTED] (b) (6). The subject received a total of 189 days of study drug. The study treatment was discontinued due to the adverse event of fractured right clavicle on day 189 [REDACTED] (b) (6). This subject previously participated in the 178-CL-047 study and was randomized to the placebo treatment. The medical history included deafness (since 1952-12-14), osteoarthritis (since 1952-12-14), right knee surgery (1965-01-01), right leg surgery (1973-01-01), nervous breakdown (1976-01-01 through 1978-01-01), left hip surgery (1980-01-01), gallstones removed (1981-01-01), left foot surgery (1985-01-01), right ankle

surgery (2002-01-01), menopause (since 2002-01-01), high cholesterol (since 2003-01-01), rash on right breast (since 2009-01-01).

On day 191, an adverse event of fractured right clavicle was reported. Study drug was reported as discontinued on day 189. The event of fractured right clavicle was reported as recovering at day of last study visit (day 212). While it was stated the event was coincidental, there are no details as to the circumstances of the injury.

Reviewer's Comment: There are insufficient details to elucidate a relationship to mirabegron in this case. The patient did have a history of left and right lower extremity surgeries, which may have played a role. Fracture was considered with other fractures and accidental injuries in the summary of safety. The conclusion is that there is not a difference in the incidence of accidental injuries in the treatment arms.

Subject 3102-2349: Paresthesia: The subject is a 48 year old white Slovakian female randomized to mirabegron 50 mg on 3 February 2009. The subject received a total of 136 days of study drug. The study treatment was discontinued due to the adverse event of paresthesia of upper and lower extremities on day 136 (2009-06-18). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg. The medical history included epilepsy (since 1963), hypertension (since 1997), allergy to duomox – amoxicillin (since 2005), depression (since 2006), gonarthrosis of the right knee (since 2008-06), and overactive bladder (since 1998). The patient is maintained on valproic acid for epilepsy.

On day 83, an adverse event of exanthema of face and chest associated with dust allergy was reported. This was attributed to a dust allergy and responded to glucocorticoid therapy.

On Day 128, adverse events of paresthesias of upper and lower extremities were reported. The subject had no relevant medical history. Study drug was discontinued on day 136 due to this event. No concomitant medications were noted due to the adverse event of paresthesias of upper and lower extremities. The adverse visit was ongoing at the time of study completion (Day 142).

Reviewer's Comment: There are sensory components to certain forms of epilepsy. Paresthesias, in the Sponsor's opinion, could also be a manifestation of hypersensitivity.

Subject 3193-3085: Supraventricular extrasystoles: Ventricular Extrasystoles: The subject is a 66 year old white Finish male randomized to mirabegron 50 mg on [REDACTED]^{(b) (6)}. The subject received a total of 294 days of study drug. The study treatment was discontinued due to the adverse events of supraventricular ectopic beats and ventricular bigeminy on Day 294 [REDACTED]^{(b) (6)}. This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg. The medical history included supraventricular ectopic beats (since 1990), ventricular bigeminy (since 1990). There were no ongoing medications.

On day 175, adverse events of supraventricular ectopic beats and ventricular bigeminy were reported. The subject had a relevant medical history of supraventricular ectopic beats and ventricular bigeminy since 1990. Study drug was discontinued on day 294 due to these adverse events. No additional information was documented regarding these events. At the time of study completion, the outcome of these adverse events of supraventricular ectopic beats and ventricular bigeminy were unknown. The investigator considered these adverse events to be mild and possibly related to study drug. The screening (day -22) ECG findings were considered normal, however the day 175 and day 315 ECG findings were considered abnormal for frequent ventricular premature complexes (>2). While the patient is reported as hypertensive on Day -22, office blood pressures were 150/94 mmHg at Baseline, 147/78 mmHg at Month1, 139/78 at Month 3 and 130/75 at Month 6.

Reviewer's Comment: With the confounding history and lack information of the normal patterns of occurrence of the patient's arrhythmias, a causal association of these events with mirabegron is confounded.

Subject 3201-3011: Hypertension: The subject is a 64 year old white Danish male randomized to mirabegron 50 mg on 17 March 2009. The subject received a total of 352 days of study drug. The study treatment was discontinued due to the adverse event of hypertension on day 352 (2010-03-03). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg treatment group. The medical history included colon cancer (2002 through 2007) and back pain (2009-02-02 through 2009-02-14). There were no medications at the time of the event.

On day 348, adverse events of hypertension and musculoskeletal related chest pain were reported. The subject had no relevant medical history; however the average systolic BP at visit 1 was greater than 150 mmHg. On day 350, the subject was given enalapril orally for a total daily dose of 20 mg for the indication of hypertension and nitroglycerin sublingually as needed for the indication of chest pain. Study drug was interrupted for an unknown period of time for the adverse event of chest pain and on day 352, study drug was discontinued due to the adverse event of hypertension. No vital sign data was available for day 348. Both screening and treatment ECGs were considered abnormal with either left anterior hemiblock or first degree AV block. At the time of study completion, the adverse event of hypertension was reported as ongoing and on day 351, the adverse event of musculoskeletal chest pain was reported as resolved.

Reviewer's Comment: We do not know the blood pressure on Day 348. On Day -22, the average systolic blood pressure was 154.6 mmHg and the average diastolic blood pressure was 84.3 mmHg. On Day -3, the respective values were 152 mmHg and 74 mmHg. On Day -1, the respective blood pressure values were 151.3 mmHg systolic and 81.3 mmHg diastolic. On Day 266 (the day closest before the event) the blood pressures were 140 mmHg systolic and 74.8 mmHg diastolic. During the clinical trial the patient's blood pressure was variable. Since the blood pressure on Day 348 is unknown, it is not possible to determine if this was an exacerbation of pre-existing labile hypertension. I do not consider this event new onset hypertension.

Subject 3275-2937: Hyperkalemia: BUN Increased: Creatinine Increased: The subject is a 70 year old white Italian female randomized to mirabegron 50 mg on 25 February 2009. The subject received a total of 196 days of study drug. The study treatment was discontinued due to the adverse events of hyperkalemia, high level of blood urea nitrogen (BUN) and high level of creatinine on day 196 (2009-09-08). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg. The medical history included diabetes (since 1990), hysterectomy (1997), vaginal reconstruction (1997). Concomitant medication are metformin and acetylsalicylic acid.

On Day 188, an adverse event of hyperkalemia was reported and on Day 189, the adverse events of elevated BUN and elevated creatinine were reported. The subject had a relevant medical history of diabetes. The adverse events of elevated BUN and creatinine were reported as ongoing at the time of final visit. Study drug was withdrawn on Day 196 due to the adverse events of hyperkalemia, elevated BUN and elevated creatinine. A clinically significant change in potassium was reported on Day 188 and returned to within normal range on Day 217. The subject's BUN and creatinine were elevated throughout the study, but were not considered clinically significant until Day 188. The subject's BUN and creatinine remained elevated at the time of final visit (Day 265). Relevant laboratory results are reported in Table 2. On Day 271, the adverse event of hyperkalemia was reported as resolved.

Study Day	Potassium (normal range 3.7 – 5.4 mmol/L)	Blood Urea Nitrogen (normal range 2.5 – 7.5 mmol/L)	Creatinine (normal range 0 – 85.748 umol/L)
-15	4.7	8.6	99.9
34	4.9	8.6	98.1
188	6.5	11.4	113.2
217	4.7	10.0	114.9
265	4.9	13.9	121.1

Source: 3275-2937 patient narrative

Reviewer's Comment: The changes in BUN and creatinine shown in the preceding table are generally modest. The BUN and creatinine decreased upon stopping mirabegron, but later (on day 265 – more than 2 months after stopping mirabegron), the BUN and creatinine increased again and were actually higher than the Day 188 values prior to stopping mirabegron. It is possible that these small changes in BUN and creatinine are related to the patient's background diabetes mellitus, or to fluid balance issues.

Subject 3285-2886: Hypersensitivity: The subject is a 71 year old white Italian female randomized to mirabegron 50 mg on 11 March 2009. The subject received a total of 167 days of study drug. The study treatment was discontinued due to the adverse event of allergic reaction on day 167. This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. The medical history included allergic asthma (since 1960), cervical fracture (2002 through 2002-11). There were no concomitant medications.

On an unknown date in 2009-08, an adverse event of allergic reaction was reported. The subject had a relevant medical history of allergic asthma. The subject consulted a dermatologist who recommended study drug be stopped. Subject was discontinued from study drug on Day 167 due to the adverse event of allergic reaction. The subject was treated with oral rupatadine 10 mg (an oral antihistamine) daily (since Day 169) for the indication of allergy. Pertinent negatives included no reported constitutional symptoms, eosinophilia or elevations in liver chemistries. On Day 190, the subject evidenced clinically significant changes of the skin due to allergic reaction. The allergic reaction was localized on both arms and legs and the subject had red scattered spots along the upper and lower limbs that were mild in severity. The rash was associated with pruritus and periorbital edema. Laboratory assessment did not reveal any abnormal values for serum albumin, protein or renal indices for day 190. The adverse event of allergic reaction was reported as resolved on an unknown date in 2009-09.

Reviewer's Comment: While the event on Day 167 may represent a drug hypersensitivity reaction to mirabegron, clinical details of the day 167 event are not provided. Further, it is of interest that the patient experienced a well-documented hypersensitivity reaction on Day 190 – approximately 23 days after stopping mirabegron.

Subject 3292-2363: Hypertension: The subject is a 28 year old white British female randomized to mirabegron 50 mg 6 February 2009. The subject received a total of 312 days of study drug. The study treatment was discontinued due to the adverse event of hypertension on day 312 (2009-12-14). This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment group with the same assigned subject number. The medical history included eczema (since 2002-06), hay fever (since 2002-06), tonic-clonic seizure (2007-05-12). Concomitant medications at the time of event were fexofenadine and ethinylestradiol/gestodene.

On day 179, an adverse event of hypertension was reported. The subject had no relevant medical history. Study drug was withdrawn on day 312 due to the adverse event of hypertension. No concomitant medications were noted due to this event. Baseline vital signs assessment showed a maximum systolic blood pressure (SBP) of 144 mmHg (day -3) and a maximum diastolic blood pressure (DBP) of 93 mmHg (day -2). On day 179, repeat afternoon blood pressures of 131/104, 134/95, and 144/99 mmHg were recorded by office device; immediately preceding measurement by home device revealed a maximum SBP of 129 mmHg and a maximum DBP of 97 mmHg. At subsequent visits, the subject evidenced occasional blood pressure measurements greater than 140/90 mmHg. Average vital signs are reported in Table 2. The subject's ECG findings were reported as normal throughout the study. The adverse event of hypertension was reported as ongoing at the time of final visit (day 320).

Clinical Review
{Insert Reviewer Name}
{Insert Application Type and Number}
{Insert Product Trade and Generic Name}

Visit / Device	Blood Pressure (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	133/84	96
Baseline: Office Device	125/78	93
Month 1: Home Device	120/94	94
Month 1: Office Device	132/92	93
Month 3: Home Device	119/85	92
Month 3: Office Device	121/93	91
Month 6: Home Device	128/95	78
Month 6: Office Device	139/97	83
Month 9: Home Device	130/109	105
Month 9: Office Device	127/102	102
Visit 7: Home Device	127/93	87
Visit 7: Office Device	126/82	83

Source: Patient Narrative 3292-2363.

The average blood pressures on Day -2 were 131 mmHg systolic and 87 mmHg diastolic. On Day -1 the respective values were 128 mmHg systolic and 84 mmHg diastolic.

There were blood pressures determined on Days 269, 270, and 271. The average blood pressures on those days respectively were 130/90, 123/90, and 127/102 mmHg. The patient was also noted to have a short systolic heart murmur noted Day-14 to Day 320 and not thereafter.

Reviewer's Comment: This patient had pre-hypertensive blood pressures noted prior to drug exposures. On Day 170, the diastolic BP appeared to worsen. On subsequent measurements, the diastolic blood pressures appeared to increase further. I would not classify this case as new onset hypertension but worsening of pre-existing hypertension in association with mirabegron use.

Subject 1624-6696: Trigeminal Neuralgia: The subject is a 69 year old white US female randomized to mirabegron 100 mg on 3 November 2008. The subject received a total of 59 days of study drug. The study treatment was discontinued due to the adverse event of trigeminal neuralgia on day 59 (2008-12-31). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group. The medical history included tonsillectomy (1955), allergies to aspirin, morphine and sulfa (since 1960), hysterectomy (1976), heart valve prolapse (since 1978), migraines (since 1978), sinus headaches (since 1978), tension headaches (since 1978), diverticulitis (since 1982), hypertension (since 1982), stomach ulcer (1982), gastroesophageal reflux disease (since 1988), recurrent sinusitis (since 1988), anxiety (since 1990), depression (since 1990), cholecystectomy (1997), irritable bowel syndrome (since 1998), hiatal hernia (since 2003), insomnia (since 2005), esophageal spasms (since 2007), osteoarthritis (since 2007), cataracts (2008), abnormal liver function tests (2008-09-24 through 2008-10-03). Concomitant medications include diphenoxylate, omeprazole, zolpidem, cyclobenzaprine and triamterene/hydrochlorothiazide.

On Day 17, an adverse event of trigeminal neuralgia was reported. The subject had a relevant medical history of tension headaches, sinus headaches and migraines. Study drug was

discontinued due to the adverse event of trigeminal neuralgia on Day 59. The subject was treated with oral gabapentin 900 mg daily (Day 17 through Day 59) for the indication of trigeminal neuralgia. No clinically significant laboratory results or physical examination findings were reported. The adverse event of trigeminal neuralgia was reported as ongoing at the time of final visit (Day 85).

Reviewer's Comment: This case is confounded as trigeminal neuralgia, tension headaches, sinus headaches and migraines may have similar underlying vascular pathophysiology.

Subject 1636-8100: Abdominal Pain: The subject is a 67 year old white US male randomized to mirabegron 100 mg 10 December 2008. The subject received a total of 25 days of study drug. The study treatment was discontinued due to the adverse event of abdominal pain on day 25 (2009-01-03). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group with the same assigned subject number. The medical history included allergy to sulfa drugs (since 1978-01-01), rheumatoid arthritis (since 1992-06-06), irritable bowel syndrome (since 1998-01-01), microwave procedure for benign prostatic hyperplasia (2004-07-22), GERD (since 2006-05-30), 2-cm presumed duodenal diverticulum (since 2006-08-17), prostatic calcification (since 2006-08-17), sigmoid diverticulosis (since 2006-08-17), small hiatal hernia (since 2006-08-17), bladder cystoscopy with biopsy (2007-06-28), mild gastritis (since 2008-05-30), benign prostatic hyperplasia (since 2008-06-09). No concomitant medications were reported.

On day 4, an adverse event of abdominal pain was reported. Relevant medical history included irritable bowel syndrome since 1998, GERD, presumed duodenal diverticulum, sigmoid diverticulosis, and small hiatal hernia since 2006, and mild gastritis since 2008. There were no physical examination findings or vital signs reported on this day. There was no concomitant treatment given for this event. The study drug was discontinued due to the adverse event of abdominal pain on day 25. The event was reported as resolved on day 29.

Reviewer's Comment: This case is confounded by multiple ongoing gastrointestinal disorders. There was resolution of pain, however, with drug dechallenge.

Subject 2178-6965: Palpitations: The subject is a 44 year old white US female randomized to mirabegron 100 mg on 9 December 2009. The subject received a total of 262 days of study drug. The study treatment was discontinued due to the adverse events of heart palpitations on day 262 (2009-08-27). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group. The medical history included no depth perception (since 1964-03-25), strabismus (1964-03-25 through 1972), strabismus surgeries (1964-03-25 through 1972), aspirin drug allergy (since 1974), penicillin drug allergy (since 1974), tonsillectomy (1976 through 1979), tonsillitis (1979), bradycardia (since 1984 ECG Day - 19 interpreted as normal with HR 53 bpm), oophorectomy (1987), ruptured ovarian cyst (1987), darvocet (propoxyphene and acetaminophen) drug allergy (since 1988), prolapsed uterus (1993 through 2004), bladder suspension (1995), prolapsed bladder (1995), neuroma right foot (2001-

10), hyperopia (since 2004), hysterectomy (2004), Gilbert's disease (since 2006-09-27). Concomitant medications include glucosamine/chondroitin sulfate, multivitamins, and glutamic acid. She received influenza vaccine on Day 7.

On day 102, an adverse event of increased heart rate was reported. No relevant cardiac medical history was reported for this subject. Heart rate measurements for the day of the event were not provided. The subject experienced three episodes of heart palpitations on days 151, 207 and 261 respectively. Study drug was discontinued due to the event of heart palpitations that occurred on day 261. No concomitant medications were noted for these events. ECG results at baseline and day 185 were reported as normal. An additional ECG performed on day 269 revealed abnormal results interpreted as sinus bradycardia. The adverse events of heart palpitations were reported as resolved on days 151, 207 and 261 respectively. Vital Sign averages are below.

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	97/63	67
Baseline: Office Device	102/55	68
Month 1: Home Device	108/60	71
Month 1: Office Device	111/49	73
Month 3: Home Device	104/69	61
Month 3: Office Device	106/50	71
Month 6: Home Device	105/71	64
Month 6: Office Device	117/54	62
Month 9: Home Device	111/69	48
Month 9: Office Device	112/62	44

Source: Patient narrative 2178-6965

Reviewer's Comment: On no occasion was documentation of a pulse change or abnormality obtained. The pulse rate appears to have decreased during the clinical trial. The palpitations resolved while patient continued on mirabegron on two occasions.

Subject 2200-6450: Palpitations: The subject is a 46 year old white Canadian female randomized to mirabegron 100 mg on 18 November 2008. The subject received a total of 24 days of study drug. The study treatment was discontinued due to the adverse event of intermittent palpitations (no other symptoms) on day 24. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group. The medical history included mitral valve prolapse (since 1993), anxiety (since 2005-04), cystoscopy (2007-11-09), environmental allergies (since 2008-03-29). Concomitant medications include escitalopram and loratadine.

On day 9, an adverse event of intermittent palpitations (no other symptoms) was reported. The subject had a relevant medical history of mitral valve prolapse and anxiety. No pulse rates were reported on day 9. No concomitant medications were noted for this event and on day 24, study

drug was discontinued due to the adverse event of intermittent palpitations. The ECGs on Days - 14 and 29 were reported as normal with heart rates of 70 and 60 bpm respectively.

Reviewer's Comment: There is no past history of palpitations despite mitral valve prolapse and anxiety. Therefore, these conditions are not plausible alternative explanations. Despite the symptom of palpitations, there is no documented rapid heart rate on study days prior to or after Day 1.

Subject 2205-7095: Headaches and Vertigo: The subject is a 46 year old white Canadian female randomized to mirabegron 100 mg 16 December 2008. The subject received a total of 87 days of study drug. The study treatment was discontinued on day 87 (2009-03-12) due to the adverse events of worsening of vertigo and worsening of headache. This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 100 mg treatment group. The medical history included appendectomy (1979-07-01), cesarean section (1980-07-07), hypothyroidism (since 1988-01-01), allergy to Demerol (meperidine) (since 1990-01-01), intermittent headaches (since 1995), encephalitis (1995-07-01), asthma (since 2002-06-01), gastroesophageal reflux disease (since 2008-05-01). Concomitant medications include levothyroxine, fluticasone inhaler, montelukast, salbutamol inhaler, paracetamol and esomeprazole.

On day 5, adverse events of headache and vertigo were reported. The subject was treated with betahistine orally for a total daily dose of 16 mg for the indication of vertigo (since an unknown date in 2009-01). On day 36, the adverse events of headache and vertigo were reported as resolved. On day 37, adverse events of worsening of vertigo and worsening of headache were reported. Study drug was discontinued on day 87 due to the adverse events of worsening of vertigo and worsening of headache. The subject was treated with oral paracetamol/codeine/caffeine as needed (beginning on day 37) for the indication of headache. There were no reported clinically significant changes in laboratory results or physical examination findings. The adverse events of worsening of vertigo and worsening of headache were reported as unresolved at the time of final visit (day 87).

Reviewer's Comment: Vertigo was not reported in Study 178-CL-047. While intermittent headaches can be considered a confounder, they were present during participation in Study 047.

Reviewer's Comment: The patient has a history of intermittent headaches and encephalitis. It is notable that the vertigo and worsening of headaches was still present on Day 87 – approximately 50 days after stopping mirabegron.

Subject 2205-7095: Edema Peripheral: The subject is a 51 year old white Canadian female randomized to mirabegron 100 mg 18 March 2009. The subject received a total of 21 days of study drug. The study treatment was discontinued due to the adverse event of edema bilateral hands on day 21 (2009-04-07). This subject previously participated in the 178-CL-047 study and was randomized to the mirabegron 50 mg treatment group. The medical history included hysterectomy (1970-01-01), pulmonary embolism (1970-01-01), scarring of lower right lung (since 1970-01-01), cholecystectomy (1975-01-01), right carpal tunnel syndrome (1999-12-01),

abdominal cavity cysts (since 2000-01-01), left carpal tunnel syndrome (2000-03-01), hypertension (since 2006-01-01), acid reflux (since 2007-01-01). Ongoing medications include acetylsalicylic acid, nifedipine, hydrochlorothiazide/irbesartan, omeprazole, multivitamins, hypericum perforatum, and ginkgo biloba.

On Day 3, an adverse event of edema bilateral hands was reported. The subject had no relevant medical history; however, the investigator stated that the subject had a previous event of edema (site[s] unspecified) while prescribed tolterodine (unspecified dates for tolterodine use) and suspected the subject may be taking tolterodine again. On Day 21, study drug was discontinued due to the adverse event of edema bilateral hands. No concomitant medications were noted for this event. Coincident with the event, there no liver function test or eosinophil count changes. The event was reported as ongoing on Day 22 (last visit).

Reviewer's Comment: The patient has a history of bilateral carpal tunnel syndrome. The reason for swelling of her hands on Day 3 is unclear.

Subject 3013-0134: Dizziness: Blurred Vision: The subject is a 69 year old white German female randomized to mirabegron 100 mg on 12 December 2008. There was no participation in previous clinical trials. The subject received a total of 90 days of study drug. The study treatment was discontinued due to the adverse events of dizziness and fuzzy sight, blurred on day 90 (2009-03-11). The medical history included tension-free vaginal taping (1999), arterial hypertension (since 2004). Concomitant medication was metoprolol.

On day 77, the events of dizziness and fuzzy sight, blurred (vision) were reported. The subject had a relevant medical history of hypertension; however, there were no appreciable blood pressure changes noted during the clinical trial to Day 79 and in the blood pressure determinations prior to Day 1. Physical examination findings were normal. No concomitant medications were used to treat the events. There were no fluctuations in vital signs during the study and all laboratory results remained within normal limits. Study drug treatment was discontinued on day 90 due to the events of dizziness and fuzzy sight, blurred vision. These events were reported as ongoing at the last evaluation (day 90).

Reviewer's Comment: There is a reasonable temporal relationship between the event and mirabegron use. Whether discontinuation of mirabegron led to resolution of the events is not stated.

Subject 3018-1402: Abdominal Pain: The subject is a 73 year old white German female randomized to mirabegron 100 mg on 2 December 2009. The subject received a total of 288 days of study drug. The study treatment was discontinued due to the adverse event of unspecific abdominal pain on day 288 (2009-09-15). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg treatment group. The medical history included Parkinson's disease (since 2007-06), kidney stones (since 2008). Concomitant medication is propranolol for Parkinson's disease.

On day 288, the adverse event of unspecific abdominal pain was reported and the subject discontinued use of the study drug treatment. The subject had a relevant medical history of kidney stones. All laboratory results remained within normal limits throughout the study with the exception of urine leukocytes that were reported as 3+ at screening (day -15) and on day 175. Alkaline phosphatase was mildly elevated at 129 U/L (normal range 31 – 121 U/L). Physical examination findings at screening (day -15) were reported as normal and at the last evaluation (day 294) the abdomen was noted by the investigator as abnormal with the finding of unspecific abdominal pain. The event was reported as resolved on day 289.

The other adverse event reported for this subject was a urinary tract infection (day 232 through day 235).

Reviewer's Comment: In the absence of known renal calculi and/or evidence of upper urinary tract obstruction, the ongoing history of kidney stones is not a significant confounding factor. The patient did have a UTI on Days 232-235 and this event of abdominal pain was reported on Day 288. It is not clear, if the abdominal pain on Day 288 representing a recurrent UTI. The abdominal pain was reported to resolve 1 day after stopping mirabegron, thus , there was a positive dechallenge to withdrawal of mirabegron.

Subject 3115-3115: Dermatitis Allergic: Pruritus: The subject is a 76 year old Polish female randomized to mirabegron 100 on 17 March 2009. The subject received a total of 101 days of study drug. The study treatment was discontinued due to the adverse events of allergic rash and itch on day 101 (2009-06-25). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 100 mg treatment group. A potential hypersensitivity narrative was also written for this subject for the event of allergy that occurred while the subject was enrolled in the 178-CL-046 study. The medical history included arthritis (since 1960), hemorrhoids (since 2000), stomach polyp (2003), stroke (2007-07-01). Ongoing medications include pantoprazole, glucosamine/chondroitin sulfate, clopidogrel, donepezil and sertraline.

On day 16, adverse events of allergic rash and pruritus were reported. The subject had no relevant medical history, however the subject had an adverse event of allergy reported during the 178-CL-046 study. On day 35, the subject began cetirizine orally for a total daily dose of 1 tablet for the indication of allergic rash and pruritus. Pertinent negatives included no constitutional symptoms or eosinophilia. The subject had a mildly elevated serum GGT (40 U/L) at baseline that remained stable. No additional elevations in liver function tests were observed. Study drug was discontinued on day 101 due to the adverse events. On day 101, the physical examination noted the allergic rash and pruritus to be changed from baseline and was considered clinically significant. No additional information regarding these events was available. The subject did consult with her personal physician prior to discontinuing from the trial. On day 115, the adverse events of allergic rash and pruritus were reported as resolved.

In Study 178-CL-046, the subject received a total of 86 days of study drug and completed the study. On day 48, an adverse event of allergy was reported. The subject had no relevant medical history. On day 48, the subject began cetirizine orally for a total daily dose of 1 tablet for the

indication of allergy. The patient continued on the study drug without worsening. Pertinent negatives included no constitutional symptoms or eosinophilia. No changes were made to study drug due to this event. On day 105, the adverse event of allergy was reported as resolved.

Reviewer's Comment: This appears to be an allergic reaction of the non-immediate type. In light of a second allergic reaction in this same patient after re-introduction of mirabegron (a positive rechallenge), a causal association is likely between the event and mirabegron.

Subject 3204-2675: Hypertension: Pelvic Pain: The subject is a 46 year old white Danish female randomized to mirabegron 100 mg. The subject received a total of 28 days of study drug. The study treatment was discontinued due to the adverse events of pelvic pain and worsening diastolic blood pressure on Day 28 (2009-04-22). This subject previously participated in the 178-CL-046 study and was randomized to the mirabegron 50 mg treatment group. The medical history included hypertension (since 1981-01). The concomitant medication was enalapril.

On Day 28, adverse events of pelvic pain and worsening diastolic blood were reported. The subject had a relevant medical history of hypertension and was taking enalapril orally for a total daily dose of 20 mg for the indication of hypertension prior to study entry. On Day 28, study drug was discontinued due to these adverse events. No changes in concomitant medications were noted for these indications. On Day 28, the subject's diastolic blood pressures were in the 100's. Prior to Day 28, the subject's diastolic blood pressures had been in the 80's -90's. The highest reported diastolic blood pressure on Day 28 was 112 mmHg. The ECGs at screening and Visit 7 (Day 83) were considered normal. On Day 64, both the adverse events of pelvic pain and worsening diastolic blood pressure were reported as resolved. No vital sign data was available on Day 64.

Reviewer's Comment: The patient had a pre-existing history of hypertension. The diastolic blood pressure appeared to increase from baseline to Day 28. This appears to be an exacerbation of pre-existing hypertension temporally associated with mirabegron use.

Subject 3221-1175: Fatigue: The subject is a 57 year old Norwegian female randomized to mirabegron 100 mg on 14 February 2009. The subject received a total of 181 days of study drug. The study treatment was discontinued due to the adverse event of fatigue on day 181 (2009-08-13). The subject received a total of 181 days of study drug. The study treatment was discontinued due to the adverse event of fatigue on day 181 (2009-08-13). The medical history included hypothyroidism (since 1971), anxiety (since 1980), migraine (since 1998), pollen allergy (since 1998), menopause (since 2001). Ongoing medications include levothyroxine, desloratadine and estradiol.

On day 138, an adverse event of fatigue was reported. The subject had a relevant medical history of hypothyroidism. No concomitant medications were given for this event. Study drug was discontinued due to this event on day 181. At the time of the last study visit, this adverse event was reported as ongoing.

Reviewer's Comment: The patient has a history of hypothyroidism. Additionally, the patient's fatigue continued after mirabegron was discontinued.

Subject 3225-2452: Memory Impairment: The subject is a 61 year old white Norwegian male randomized to mirabegron 100 mg on 12 February 2009. The subject received a total of 279 days of study drug. The study treatment was discontinued due to the adverse event of lapse of memory on day 279 (2009-11-17). This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. The medical history included fear of flying (since 1960), frequent defecation (since 1990), lactose intolerance (since 1999), dry mouth (since 2008-12-15). Concomitant medications include oxazepam prn and plantago afra/sodium chloride/thiamine (frequent defecation).

On Day 81, an adverse event of lapse in memory was reported. No relevant medical history was noted. The subject also experienced adverse events of mild depression (Day 79 through Day 154) and severe global amnesia (Day 80 through Day 81) that were considered by the investigator to be possibly related to study drug. No concomitant medications were given for the adverse event of lapse in memory and on Day 279, study drug was discontinued due to this adverse event. At the time of study completion, the adverse event of lapse in memory was reported as not resolved.

Additional adverse events reported for this subject included pain in both knees (on Day 33 and was not resolved at the time of study completion), pain in left side of throat (Day 61 through Day 99), and a common cold (Day 175 through 178).

Reviewer's Comment: The patient's mild depression and severe global amnesia resolved while patient continued on mirabegron, but the lapse in memory did not. It is notable that the patient was also taking oxazepam at baseline. It is also to be noted that in the tolterodine 4 mg SR arm, there is one report of global amnesia (3102-2210), one report of memory impairment (3192-2013) one report of cognitive disorder (3203-2013), and one report of confusional state (3298-2297).

Subject 3232-1080: Hypertension: The subject is a 65 year old Swedish female randomized to mirabegron 100 mg on 5 November 2008. The subject received a total of 73 days of study drug. The study treatment was discontinued due to the adverse event of worsening hypertension on day 73 (2009-01-16). This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment group. The medical history included allergy to sulfa (since 1970), hypertension (since 1985), fractured 2nd lumbar vertebra (2003), osteoporosis (since 2003), allergy to Zyban (bupropion) (since 2004), chronic bronchitis (since 2004). Ongoing medications include calcium carbonate, carvedilol, lercanidipine and enalapril.

On Day 31, an adverse event of worsening hypertension was reported. This subject had a relevant medical history of hypertension and was taking several concomitant medications for the indication of hypertension prior to screening. During the screening period, the subject's systolic blood pressures had transient episodes in the 180's to 190's and diastolic blood pressures had

transient episodes in the 90's to 100's. On Day 31, the subject's highest reported systolic blood pressure was 200 mmHg and the highest reported diastolic blood pressure was 117 mmHg. Throughout the study, the subject continued to have intermittent episodes of elevations in blood pressure. No changes were made to concomitant medications during this time period. All study related ECGs were interpreted as normal. On Day 73, study drug was discontinued due to this adverse event of worsening hypertension. On Day 94, the adverse event of worsening of hypertension was reported as resolved. Average Vital signs are below:

Visit / Device	BP (mmHg)	Heart Rate (beats per minute)
Baseline: Home Device	135/85	95
Baseline: Office Device	137/76	89
Month 1: Home Device	195/109	79
Month 1: Office Device	180/97	77

Source: Patient Narrative 3232-1080.

Reviewer's Comment: The patient had pre-existing hypertension and was taking three anti-hypertensive medications at baseline. The screening blood pressures were quite elevated and did not demonstrate excellent control. The on-treatment blood pressures were higher than the baseline, but similar to screening. It appears this patient may have experienced some degree of worsening of existing hypertension in association with mirabegron use.

Subject 3301-2700: QT corrected interval prolonged: The subject is a 70 year old white British female randomized to mirabegron 100 mg on 4 March 2009. The subject received a total of 14 days of study drug. The study treatment was discontinued due to the adverse event of abnormal ECG - prolonged QTc interval on day 14 (2009-03-17). This subject previously participated in the 178-CL-046 study and was randomized to the tolterodine SR/ER 4 mg treatment group. During participation in Study 178-CL-046, the events of events of abnormal ECG (prolonged QT interval) and abnormal ECG (supraventricular arrhythmia) were noted and will be discussed below.

The medical history included urinary bladder repair (procedure unknown) (1968), depression/anxiety (since 1973), hysterectomy (1976), colposuspension (1984), urinary bladder repair (1984), arthritis of spine and hips (since 2002), hiatus hernia (since 2002), right hip replacement (2002), raised cholesterol (since 2003), type 2 diabetes (diet controlled) (since 2005), fibromyalgia (since 2005), hypertension (since 2005), dry eyes (since 2006), spinal stenosis (since 2006), dry mouth (since 2008-10), and reduced range of movement of left shoulder (since 2009-01). Ongoing medications include citalopram, domperidone, esomeprazole, simvastatin, amlodipine, bendroflume thiazide, losartan, carbomer (dry eyes), fentanyl and gabapentin.

On Day 14, an adverse event of abnormal ECG (prolonged QTc interval) was reported. Relevant medical history included hypertension, type 2 diabetes, raised cholesterol and reported adverse events of abnormal ECG (prolonged QT interval and supraventricular arrhythmia) while enrolled

in 178-CL-046. The adverse event of abnormal ECG (prolonged QTc interval) was reported as unresolved at the time of final visit Day 14. On Day 14, the study treatment was discontinued due to the adverse event of abnormal ECG (prolonged QTc interval). No concomitant medications were noted for this event. The ECG interpretation at screening (day -22) was normal and the final visit (Day 14) was abnormal for left atrial enlargement and ST segment depression.

The ECG findings are below:

Study Day	HR Mean (bpm)	PR Mean (ms)	QRS Duration (ms)	RR Mean (ms)	QTcF Mean (ms)	QTcB Mean (ms)	QT Mean (ms)	ECG Interpretation	Comments
-22	73	183	83	822	418	432	392	normal	-
14	81	184	76	742	432	454	391	abnormal	left atrial enlargement, ST segment depressed

Source: Patient Narrative 3301-2700: 178-CL-049

While enrolled in 178-CL-046, the subject received 84 days of tolterodine ER/ SR 4mg and had adverse events of abnormal ECGs (prolonged QT interval and supraventricular arrhythmia) reported on day 84. By Day 118, both events had resolved. The ECG findings are below:

Study day	HR Mean (BPM)	PR Mean (ms)	QRS duration (ms)	RR Mean (ms)	QTcF Mean (ms)	QTc B Mean (ms)	QT Mean (ms)	Overall ECG Interpretation	Comments
-22	71	169	85	849	434	446	411	Abnormal	Left atrial enlargement
84	80	185	84	749	441	463	400	Abnormal	Left atrial enlargement

Source: Patient Narrative 3301-2700: 178-CL-046

Reviewer's Comment: In this study, the pre-treatment and post-treatment QTcF differ by 14 msec. In the previous study, the difference was 7 msec. Neither of these corrected QT intervals (QTcF and QTcB) changes from baseline exceed 30 msec. It is notable that mild increases in QT occurred while patient was taking each drug (mirabegron and tolterodine) which may imply a background propensity in this elderly female.

Reviewer's Comment: In the category of AEs resulting in study discontinuation, the notable findings include:

- There a single events in the mirabegron 50 mg arm of atrial flutter (fibrillation), versus one case of atrial fibrillation in the mirabegron 100 mg arm and two cases of atrial fibrillation in the tolterodine SR 4 mg arm.*
- There are several cases of worsening of pre-existing hypertension in mirabegron-treated patients.*
- There was at least one case of pruritis/rash apparently related to mirabegron.*

- *Seven patients in the mirabegron 50 mg discontinued with listed event of constipation, in the mirabegron 100 mg group two patients discontinued with the listed AE of constipation and in the tolterodine SR 4 mg group no patient discontinued with the listed AE of constipation.*
- *Dizziness, nausea, blurred vision, dry eyes and UTI were reported as reasons for discontinuation in < 1% of subjects, but at modestly higher incidences for mirabegron compared to tolterodine.*

Clinical Laboratory

Hematology

With the exception of leukocyte count, mean changes from baseline to each visit in hematology variables were similar across the treatment groups. Mean decreases from baseline to month 1 and month 6 in leukocyte count were observed in the mirabegron 50 mg ($-0.19 \times 10^9/L$ and $-0.29 \times 10^9/L$, respectively) and mirabegron 100 mg ($-0.32 \times 10^9/L$ for both visits) groups. In the tolterodine ER 4 mg group, leukocyte count at month 1 and month 6 was similar to baseline (change from baseline: $-0.01 \times 10^9/L$ for both visits). The decreases in leukocyte count at month 1 and month 6 in the mirabegron groups were not progressive; at month 12, the mean change from baseline in leukocyte count was $-0.23 \times 10^9/L$ in both the mirabegron 50 mg and mirabegron 100 mg groups, compared to $-0.19 \times 10^9/L$ in the tolterodine ER 4 mg group. One patient 3151-1822 had neutrophil counts of 3110, 550, 3660 and 1930 $\times 10^6/L$ on Days -15, 29, 169 and 359 respectively. A total of 7 patients were found to have an absolute neutrophil count $< 1000 \times 10^6/L$ at any visit, 0.2 % (2/812) in the mirabegron 50 mg group, 0.2 % (2/820) in the mirabegron 100 mg group and 0.4% (3/812) in the tolterodine ER 4 mg group. All 7 patients completed all visits. One patient had an absolute neutrophil count $< 1000 \times 10^6/L$ at baseline (mirabegron 50 mg group), 3 patients at month 1 (1 in each treatment group), with normalization thereafter and 3 patients at month 12 (1 in the mirabegron 100 mg group and 2 in the tolterodine ER 4 mg group). In all 7 patients, an absolute neutrophil count $< 1000 \times 10^6/L$ occurred only at one occasion.

With the exception of hematocrit, shifts below the LLN or above the ULN in hematology variables were similar across the treatment groups; the majority of patients had no change from baseline to the Final Visit. The incidence of shifts in hematocrit from normal at baseline to below the LLN at Final Visit was 1.9% in the mirabegron 50 mg group, 2.9% in the mirabegron 100 mg group and 0.8% in the tolterodine ER 4 mg group. This was not accompanied by a similar trend in hemoglobin, all three groups displayed similar incidence of shifts from normal at baseline to low at Final Visit.

In general, hematology values that met PCS criteria did not have a close temporal relationship to TEAEs. Of the 35 patients with platelet counts $< 120 \times 10^9/L$ 1 patient in the mirabegron 50 mg group (Patient No. 1651-6975: platelet count of $139 \times 10^9/L$ on Day -16, $125 \times 10^9/L$ on Day 30 and $104 \times 10^9/L$ on Day 185) and 1 patient in the tolterodine ER 4 mg group (Patient No. 1604-6740) had a TEAE of platelet count decreased

(PT) reported at the time the PCS criterion was met. Two additional patients with platelet counts < 120 x 10⁹/L (Patient No. 2037-0516 in the mirabegron 100 mg group [the low platelet count was observed in association with an SAE report of hemolytic anemia and potential hypersensitivity SAE: see narrative] and Patient No. 3382-0408 in the tolterodine ER 4 mg group) experienced corresponding TEAEs of thrombocytopenia.

Table 45: PCS Thrombocytopenia Incidence in Study 178-CL-049

Platelet < 120 x 10 ⁹ /L Category	Mirabegron 50 mg N=812	Mirabegron 100 mg N=820	Tolterodine ER 4 mg N=812
Total Subjects Listed	11	13	6
Low Baseline and Low Count on Drug	6	4	2
Baseline <120 x 10 ⁹ /L	2	2	0
Isolated Low Count on Drug (not last)	2	4	2
Normal baseline and Low Count at Endpoint	4	5	3
Baseline >120 x 10 ⁹ /L and Low Count at Endpoint	6	6	3
Two or more low counts on Drug	4	3	1
Two or more low counts on Drug with normal Baseline	0	1	1
Two or more low counts on Drug with low Baseline 120-145 x 10 ⁹ /L	1	1	1

Low baseline platelets = <145 x 10⁹/L

Sources: Table 6 List of Patients with PCS Chemistry Variables, Attachment 2, Study Report 178-CL-049

Reviewer's Comment: The difference between groups in total PCS decreases in platelets between mirabegron and tolterodine is small. One patient in the mirabegron 100 mg group had an associated hypersensitivity reaction otherwise there no associated adverse events in these subjects. These results do not seem to be clinically significant and therefore do not raise a safety concern in my opinion.

Clinical Chemistry

With the exception of serum GGT, shifts below the LLN or above the ULN in serum chemistry

variables were similar across the treatment groups . A total of 47 (7.2%) patients in the mirabegron 50 mg group, 39 (5.8%) patients in the mirabegron 100 mg group and 32 (4.8%) patients in the tolterodine ER 4 mg group had a shift in serum GGT from normal at baseline to above the ULN at Final Visit. Of these patients with GGT shifts, 24 of 47 (51.1%) patients in the mirabegron 50 mg group, 12 of 39 (30.8%) patients in the mirabegron 100 mg group and 10 of 32 (31.3%) patients in the tolterodine ER 4 mg group had accompanying elevations of other hepatic function parameters; the remaining patients with GGT shifts had elevations in GGT only. When extreme values were considered rather than Final Visit, shifts in GGT from normal at baseline to above the ULN occurred in 76 (11.7%) patients in the mirabegron 50 mg group, 67 (9.9%) patients in the mirabegron 100 mg group and 55 (8.3%) patients in the tolterodine ER 4 mg group. Of these patients with GGT shifts, 47 of 76 (61.8%) patients in the mirabegron 50 mg group, 32 of 67 (47.8%) patients in the mirabegron 100 mg group and 23 of 55 (41.8%) patients in the tolterodine ER 4 mg group had accompanying elevations of other hepatic function parameters; the remaining patients with GGT shifts had elevations in GGT only.

The incidence of patients whose treatment-emergent potassium levels met the PCS criterion of > 5.6 mmol/L was 14 (1.8%), 5 (0.6%) and 4 (0.5%) in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. The highest potassium value on treatment was 7.9 mmol/L for a patient in the mirabegron 50 mg group, 6.1 mmol/L for a patient in the mirabegron 100 mg group and 6.1 mmol/L for a patient in the tolterodine ER 4 mg group. Among the 14 patients in the mirabegron 50 mg group: 12 patients were female; 1 patient had a high potassium value above the ULN at baseline; 3 patients had potassium values that met the PCS criterion on the last study day; and 3 patients had TEAEs reported (Patient No. 1598-6956 [potassium 5.6 mmol/L at baseline], hyperkalemia; Patient No. 3115-3224, blood potassium increased [had increased creatinine]; and Patient No. 3275-2937, hyperkalemia [in association with increased BUN and creatinine: drug withdrawn Day 88 : history of diabetes]).

No patient in the mirabegron 50 mg or 100 mg groups had a serum creatinine value that met the PCS criterion (creatinine >177mcmol/L). The incidence of patients whose BUN value met the PCS criterion was 0.4% (3/792), 0.9% (7/803) and 1.0% (8/791) in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg groups, respectively. Most patients with a BUN value that met the PCS criterion had a history of diabetes, hypertension or renal insufficiency. Most of these patients had evidence of elevation in BUN and/or creatinine prior to starting double-blind study drug. No patient in the mirabegron 50 mg or 100 mg groups had a serum BUN value that met the PCS criteria (BUN > 12.5mmol/L). Patient No. 3275-2937 (history of diabetes: see discontinuation narrative) in the mirabegron 50 mg group discontinued study drug due to TEAEs of blood creatinine increased and blood urea increased; however, none of the values for BUN or creatinine met the PCS criteria.

1 patient (Patient No. 3353-1381) in the mirabegron 50 mg group met laboratory criteria for Hy's Law (i.e., concomitant elevations in ALT and/or AST > 3 times the ULN [ULN=39 U/L] and total bilirubin > 2 times the ULN [ULN=18.6 mcmol/L]) on Day 185. AST values were 85 U/L at baseline and 120 U/L on Day 185; bilirubin values were 22.6 mcmol/L and 42.1 mcmol/L for the same respective time points. This patient experienced a TEAE of hepatic enzyme increased on Day 36. The event was mild and considered not related to the study drug. This patient had

ongoing hepatitis B and a past history of alcoholism. Given the ongoing viral hepatitis as an alternate etiology, this case is ruled out as a case of Hy's law due to mirabegron.

Table 46: Hepatic Serum Chemistries Values Meeting Potentially Clinically Significant Criteria Study 178-CL-049

Hepatic Function	PCS Criteria	Mirabegron 50mg n=812	Mirabegron 100mg n=820	Tolterodine ER 4mg n=812
		n/n (%)		
ALT (U/L)	>3 x ULN	8/792 (1.0%)	8/803 (1.0%)	6/792 (0.8%)
	>5 x ULN	1/792 (0.1%)	3/803 (0.4%)	1/792 (0.1%)
	>10 x ULN	1/792 (0.1%)	0	0
AST (U/L)	>3 x ULN	6/792 (0.8%)	5/803 (0.6%)	3/792 (0.4%)
	>5 x ULN	2/792 (0.3%)	2/803 (0.2%)	0
	>10 x ULN	2/792 (0.3%)	0	0
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%)	3/792 (0.4%)
ALT and/or AST (U/L) and Total Bilirubin (mcmol/L)	>3 x ULN And >2 x ULN	1/792 (0.1%)	0	0
GGT (U/L)	>100 U/L	27/792 (3.4%)	23/803 (2.9%)	24/791 (3.0%)

Source: Table 48, 178-CL-049 Study Report, page 188

Reviewer's Comment: The outliers noted in hepatic function tests do not indicate a significant clinical trend or safety concern for the overall study population when comparing mirabegron to tolterodine.

The incidence of shifts from negative to positive in urine glucose at Final Visit was 2.2% (15/678), 1.8% (13/714) and 1.4% (10/698) for the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. With respect to urine protein, in the 50 mg mirabegron group the number of subjects who had an increase over baseline in urine protein was 4/242 (1.3%) and in the 100 mg mirabegron group the number was 6/249 (2.4%). The comparable number for tolterodine ER 4 mg was 4/253 (1.6%).

Vital Signs

Overall, a small increase in mean pulse rate was observed across all treatment groups for both AM and PM measurements. This increase appeared to be dose dependent for the mirabegron groups at both the AM and PM measurements. Changes in mean AM and PM SBP and DBP measurements were not clinically meaningful and were comparable across all treatment groups.

Table 47: Overview Changes From Baseline to Final Visit in Pulse Rate Study 178-CL-049

Parameter	Mirabegron		Tolterodine
	50mg (n=812)	100mg (n=820)	ER 4mg (n=812)
Pulse Rate (bpm)			
AM			
N	791	802	812
Baseline Mean	71.0	70.2	70.1
Adjusted Mean Change from Baseline	0.9	1.6	1.5
PM			
N	789	802	792
Baseline Mean	74.2	74.1	73.8
Adjusted Mean Change from Baseline	0.4	1.3	1.9

Source: Table 49, Study Report 178-CL-049, page 191.

In the overall population, based on the repeated measures analysis, an adjusted mean change from baseline to month 1 in AM pulse rate of 0.8, 2.1 and 1.2 bpm was observed in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively; these adjusted mean changes were maintained at most subsequent time points. The adjusted mean change from baseline in AM pulse rate at the Final Visit (ANCOVA analysis) was 0.9, 1.6 and 1.5 bpm for the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. In the overall population (based on the repeated measures analysis), an adjusted mean change from baseline to month 1 in PM pulse rate of 1.1, 2.0 and 2.0 bpm was observed in patients in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. Generally, these adjusted mean changes were maintained at subsequent time points in each treatment group. The adjusted mean changes from baseline to Final Visit (ANCOVA analysis) in the PM pulse rate were 0.4, 1.3 and 1.9 bpm for the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups respectively.

A dose-dependent increase in AM and PM pulse rate was observed for the normotensive and hypertensive populations in all three treatment groups and this was generally consistent with the results for the overall population. In the normotensive population, the adjusted mean changes from baseline to Final Visit in AM and PM pulse rate, respectively, were 0.8 and 0.3 bpm for the mirabegron 50 mg group, 1.5 and 1.4 bpm for the mirabegron 100 mg group and 1.4 and 2.1 bpm for the tolterodine ER 4 mg group. In the hypertensive population, the adjusted mean change from baseline to Final Visit in AM and PM pulse rate, respectively, was 1.2 and 0.4 bpm for the mirabegron 50 mg group, 1.7 and 1.0 bpm for the mirabegron 100 mg group and 1.8 and 1.8 bpm for the tolterodine ER 4 mg group. The limited number of patients in the past history of hypertension population precludes the ability to draw formal conclusions about this population.

Table 48: AM Pulse Rate Incidence of Patients Meeting Selected Criteria Study 178-CL-049.

Parameter	Mirabegron		Tolterodine
	50mg (n=812)	100mg (n=820)	ER 4mg (n=812)
Overall Population n/n (%)			
Final Visit			
Change From Baseline \geq 10 bpm	63/791 (8.0%)	72/802 (9.0%)	68/792 (8.6%)
2 Consecutive Baseline Visits			
Change From Baseline \geq 5 bpm	154/741 (20.8%)	199/741 (26.9%)	171/735 (23.3%)
Change From Baseline \geq 10 bpm	28/741 (3.8%)	55/741 (7.4%)	44/735 (6.0%)
Change From Baseline \geq 15 bpm	10/741 (1.3%)	9/741 (1.2%)	13/735 (1.8%)
Normotensive Population	(n=488)	(n=509)	(n=478)
Final Visit			
Change From Baseline \geq 10 bpm	34/474 (7.2%)	46/498 (9.2%)	39/468 (8.3%)
2 Consecutive Baseline Visits			
Change From Baseline \geq 5 bpm	92/439 (21.0%)	123/439 (26.8%)	105/433 (24.2%)
Change From Baseline \geq 10 bpm	15/439 (3.4%)	36/459 (7.8%)	25/433 (5.8%)
Change From Baseline \geq 15 bpm	3/439 (0.7%)	7/459 (1.5%)	7/433 (1.6%)
Hypertensive Population	(n=324)	(n=311)	(n=334)
Final Visit			
Change From Baseline \geq 10 bpm	29/317 (9.1%)	26/304 (8.6%)	29/324 (9.0%)
2 Consecutive Baseline Visits			
Change From Baseline \geq 5 bpm	62/302 (20.5%)	76/282 (27.0%)	66/302 (21.9%)
Change From Baseline \geq 10 bpm	13/302 (4.3%)	19/282 (6.7%)	19/302 (6.3%)
Change From Baseline \geq 15 bpm	7/302 (2.3%)	2/282 (0.7%)	6/302 (2.0%)

Source: Table 53, Study Report 178-CL-049, page 199.

Table 49: PM Pulse Rate Incidence of Patients Meeting Selected Criteria Study 178-CL-049

Parameter	Mirabegron		Tolterodine
	50mg (n=812)	100mg (n=820)	ER 4mg (n=812)
Overall Population n/n (%)			
Final Visit			
Change From Baseline \geq 10 bpm	59/789 (7.5%)	91/802 (11.3%)	89/792 (11.2%)
2 Consecutive Baseline Visits			
Change From Baseline \geq 5 bpm	170/741 (22.9%)	247/741 (33.3%)	227/735 (30.9%)
Change From Baseline \geq 10 bpm	46/741 (6.2%)	70/741 (9.4%)	81/735 (11.0%)
Change From Baseline \geq 15 bpm	17/741 (2.3%)	14/741 (1.9%)	18/735 (2.4%)
Normotensive Population	(n=488)	(n=509)	(n=478)
Final Visit			
Change From Baseline \geq 10 bpm	38/474 (8.0%)	62/498 (12.4%)	59/468 (12.6%)
2 Consecutive Baseline Visits			

Change From Baseline ≥ 5 bpm	100/439 (22.8%)	155/459 (33.8%)	144/433 (33.3%)
Change From Baseline ≥ 10 bpm	24/439 (5.5%)	50/459 (10.9%)	47/433 (10.9%)
Change From Baseline ≥ 15 bpm	8/439 (1.8%)	10/459 (2.2%)	9/433 (2.1%)
Hypertensive Population	(n=324)	(n=311)	(n=334)
Final Visit			
Change From Baseline ≥ 10 bpm	21/315 (6.7%)	29/304 (9.5%)	30/324 (9.3%)
2 Consecutive Baseline Visits			
Change From Baseline ≥ 5 bpm	70/302 (23.2%)	92/282 (32.6%)	92/282 (32.6%)
Change From Baseline ≥ 10 bpm	22/302 (7.3%)	20/282 (7.1%)	20/282 (7.1%)
Change From Baseline ≥ 15 bpm	9/302 (3.0%)	4/282 (1.4%)	4/282 (1.4%)

Source: Table 54, Study Report 178-CL-049, page 200.

Reviewer's Comment: The changes in the AM and PM pulse rates were similar between treatment groups and lower for mirabegron 50 mg compared to tolterodine. The changes were greater for mirabegron 100 mg compared to mirabegron 50 mg, but still consistent with tolterodine. The changes in the normotensive and hypertensive populations were comparable and similar. The pulse increases were modest. The clinical significance of the pulse changes observed in the three groups cannot be stated.

No patient met the criteria for a PCS change from baseline in AM or PM pulse rate at the Final Visit or at any visit (≥ 120 bpm and ≥ 15 bpm change from baseline to Final Visit/any visit) either documented in patient diary or at office visits. The overall incidence of tachycardia defined as >100 bpm in Study 178-CL-049 was 3.1% in the mirabegron 50 mg group, 6.0% in the mirabegron 100 mg group and 6.5% in the tolterodine ER 4 mg group. Most events of tachycardia (average pulse rate > 100 bpm) using diary data were isolated in nature with no consistent pattern of worsening over time. No events of tachycardia resulted in permanent discontinuation of study drug.

Female patients in all 3 treatment groups had numerically greater increases from baseline in mean AM and PM pulse rate compared to male patients (at Final Visit). Within female patients, the changes from baseline in AM or PM pulse rate for the mirabegron treatment groups was similar to or less than the changes from baseline in the tolterodine treatment group. For final visit AM pulse rate the changes from baseline were -0.6 for males and 1.5 for females.

Dose-dependent increases in AM and PM pulse rate were observed in patients < 65 years of age and ≥ 65 years of age [Table 56 and Table 57]. In all 3 groups, the adjusted mean increase from baseline at Final Visit in AM pulse rate was numerically greater in patients < 65 years of age compared to patients ≥ 65 years of age. The adjusted mean increases from baseline in PM pulse rate in the mirabegron 100 mg dose group and tolterodine ER 4 mg group were also numerically greater in patients < 65 years of age compared to patients ≥ 65 years of age. In the mirabegron 50 mg group, the adjusted mean changes from baseline to Final Visit in PM pulse rate were similar between patients < 65 years of age and patients

≥65 years of age (for mirabegron 50 mg 1.0 bpm < 65 years of age and 0.8 for patients ≥65 years of age).

Table 50: Change from Baseline to Final Visit in Blood Pressure in Study 178-CL-049

Parameter	Mirabegron				Tolterodine	
	50 mg (n=812)		100 mg (n=820)		ER 4mg (n=812)	
Blood Pressure (mmHg)	SBP	DBP	SBP	DBP	SBP	DBP
AM						
n	791	791	802	802	812	812
Baseline mean	126.7	77.6	125.9	77.2	126.8	77.6
Mean Δ from Baseline	0.2	-0.3	0.4	0.4	-0.5	0.1
PM						
n	789	789	802	802	793	793
Baseline mean	126.4	76.2	125.7	75.9	126.3	76.1
Mean Δ from Baseline	-0.3	-0.0	0.1	0.1	-0.0	0.6

Source: Table 49, Study Report 178-CL-049, page 191.

In the overall population, based on the repeated measures analysis, the adjusted mean change from baseline to month 6 in AM SBP was -1.2, -1.0, -1.6 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively. At month 12, the adjusted mean changes were similar to month 1 (0.5, 0.5 and -0.5 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively). An adjusted mean change from baseline to Final Visit (ANCOVA analysis) in AM SBP of 0.2 and 0.4 mm Hg was observed in patients in the mirabegron 50 mg and mirabegron 100 mg groups, respectively; these values are clinically unremarkable, in the Sponsor's opinion. In the tolterodine ER 4 mg group, the adjusted mean change from baseline to Final Visit was -0.5 mm Hg.

In the overall population (based on the repeated measures analysis), an adjusted mean change from baseline to month 6 in PM SBP were -2.1, -2.1 and -1.8 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively. At month 12, these adjusted changes were -0.2, 0.3 and -0.1 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively. The adjusted mean change from baseline to Final Visit (ANCOVA analysis) in PM SBP of -0.3 and 0.1 mm Hg was observed in patients in the mirabegron 50 mg and mirabegron 100 mg groups, respectively; these values are clinically unremarkable, in the Sponsor's opinion, were not consistent with a dose-dependent response and were similar to the adjusted mean change of -0.0 mm Hg observed in the tolterodine ER 4 mg group at Final Visit.

Patients in the hypertensive subpopulation had slightly higher SBP at baseline compared to the normotensive subpopulation. The adjusted mean change from baseline to Final Visit in AM SBP was 0.0 mm Hg in the mirabegron 50 mg group and -0.4 mm Hg in the mirabegron 100 mg; the

adjusted mean change from baseline to Final Visit in PM SBP was -0.2 mm Hg for mirabegron 50 mg and -1.0 mm Hg with mirabegron 100 mg. In the tolterodine ER 4 mg group, the adjusted mean change from baseline to Final Visit in AM and PM SBP was -0.7 mm Hg and -0.1 mm Hg, respectively.

In the overall population, based on the repeated measures analysis, the adjusted mean change from baseline to month 6 in AM DBP were -0.6, -0.2 and -0.6 mm Hg, in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. At month 12, the adjusted mean changes were -0.3, 0.3 and 0.1 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively [Figure 18]. The adjusted mean change from baseline to Final Visit (ANCOVA analysis) in AM DBP of -0.3 and 0.4 mm Hg was observed in patients in the mirabegron 50 mg and mirabegron 100 mg groups, respectively; these changes were not consistent with a dose-dependent response and were similar to the adjusted mean change of 0.1 mm Hg observed in the tolterodine ER 4 mg group at Final Visit.

In the overall population (based on the repeated measures analysis), an adjusted mean change from baseline to month 6 in PM DBP of -0.8, -0.8 and -0.3 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively was observed. At month 12, the adjusted changes from baseline were 0.0, 0.1 and 0.6 mm Hg for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively. The adjusted mean change from baseline to Final Visit (ANCOVA analysis) in PM DBP of -0.0 and 0.1 mm Hg was observed in patients in the mirabegron 50 mg and mirabegron 100 mg groups, respectively; the sponsor found these changes were clinically unremarkable and were not consistent with a dose-dependent response and were similar to the adjusted mean change of 0.6 mm Hg observed in the tolterodine ER 4 mg group at Final Visit.

In the normotensive subpopulation, the adjusted mean change from baseline to Final Visit in AM DBP decreased slightly (-0.2 mm Hg) in the mirabegron 50 mg treatment group and increased in the mirabegron 100 mg treatment group (0.8 mm Hg). The adjusted mean change from baseline to Final Visit in PM DBP increased slightly with mirabegron 50 mg and mirabegron 100 mg (0.1 mm Hg and 0.4 mm Hg, respectively). In the tolterodine ER 4 mg group, the adjusted mean change from baseline to Final Visit in AM and PM DBP was 0.2 mm Hg and 0.4 mm Hg, respectively.

Patients in the hypertensive subpopulation had higher AM DBP values at baseline compared to the normotensive subpopulation, while no differences in baseline PM DBP were observed between subpopulations. In the hypertensive subpopulation, a decrease in adjusted mean change from baseline to Final Visit was observed in AM and PM DBP for both mirabegron 50 mg and mirabegron 100 mg groups (-0.4 mm Hg and -0.3 mm Hg for AM DBP, respectively and -0.2 mm Hg and -0.3 mm Hg for PM DBP, respectively); these changes are clinically unremarkable, in the Sponsor's opinion, and were not consistent with a dose-dependent response. In the tolterodine ER 4 mg group, the adjusted mean change from baseline to Final Visit in AM and PM DBP was -0.0 mm Hg and 0.9 mm Hg, respectively.

Table 51: Systolic Blood Pressure Outliers Study 178-CL-049 Summary Table

Parameter, n/n (%)	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
Overall	n=812	n=820	n=812
Final Visit AM/PM Systolic			
Change from Baseline ≥ 15 mmHg AM	52/791 (6.6%)	48/802 (6.0%)	52/791 (6.6%)
Change from Baseline ≥ 15 mmHg PM	46/789 (5.8%)	48/802 (6.0%)	46/789 (5.8%)
2 Consecutive Postbaseline Visits			
Change from Baseline ≥ 10 mmHg AM	69/741 (9.3%)	69/741 (9.3%)	61/736 (8.3%)
Change from Baseline ≥ 10 mmHg PM	68/741 (9.2%)	69/741 (9.3%)	65/736 (8.8%)
Change from Baseline ≥ 15 mmHg AM	25/741 (3.4%)	22/741 (3.0%)	29/736 (3.9%)
Change from Baseline ≥ 15 mmHg PM	20/741 (2.7%)	21/741 (2.8%)	27/736 (3.7%)
Change from Baseline ≥ 20 mmHg AM	8/741 (1.1%)	9/741 (1.2%)	10/736 (1.4%)
Change from Baseline ≥ 20 mmHg PM	7/741 (0.9%)	8/741 (1.1%)	10/736 (1.4%)
Normotensive	n=488	n=509	n=478
Final Visit AM/PM Systolic			
Change from Baseline ≥ 15 mmHg AM	24/474 (5.1%)	26/498 (5.2%)	20/469 (4.3%)
Change from Baseline ≥ 15 mmHg PM	23/474 (4.9%)	25/498 (5.0%)	26/469 (5.5%)
2 Consecutive Postbaseline Visits			
Change from Baseline ≥ 10 mmHg AM	32/439 (7.3%)	39/459 (8.5%)	30/434 (6.9%)
Change from Baseline ≥ 10 mmHg PM	33/439 (7.5%)	40/459 (8.7%)	32/434 (7.4%)
Change from Baseline ≥ 15 mmHg AM	12/439 (2.7%)	13/459 (2.8%)	13/434 (3.0%)
Change from Baseline ≥ 15 mmHg PM	11/439 (2.5%)	13/459 (2.8%)	10/434 (2.3%)
Change from Baseline ≥ 20 mmHg AM	4/439 (0.9%)	5/459 (1.1%)	2/434 (0.5%)
Change from Baseline ≥ 20 mmHg PM	2/439 (0.5%)	5/459 (1.1%)	1/434 (0.2%)
Hypertensive	n=324	n=311	n=334
Final Visit AM/PM Systolic			
Change from Baseline ≥ 15 mmHg AM	28/317 (8.8%)	22/304 (7.2%)	25/324 (7.7%)
Change from Baseline ≥ 15 mmHg PM	23/315 (7.3%)	23/304 (7.6%)	23/315 (7.3%)
2 Consecutive Postbaseline Visits			
Change from Baseline ≥ 10 mmHg AM	37/302 (12.3%)	30/282 (10.6%)	31/302 (10.3%)
Change from Baseline ≥ 10 mmHg PM	35/302 (11.6%)	29/282 (10.3%)	33/302 (10.9%)

Change from Baseline ≥ 15 mmHg AM	13/302 (4.3%)	9/282 (3.2%)	16/302 (5.3%)
Change from Baseline ≥ 15 mmHg PM	9/302 (3.0%)	8/282 (2.8%)	17/302 (5.6%)
Change from Baseline ≥ 20 mmHg AM	4/302 (1.3%)	4/282 (1.4%)	8/302 (2.6%)
Change from Baseline ≥ 20 mmHg PM	5/302 (1.7%)	3/282 (1.1%)	9/302 (3.0%)

Source: Tables 61 and 62, Study Report 178-CL-049, pages 215 and 216

Table 52: Diastolic Blood Pressure Outliers Study 178-CL-049

Parameter, n/n (%)		Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
<i>Overall</i>		n=812	n=820	n=812
Final Visit	AM/PM Diastolic			
Change from Baseline ≥ 10 mmHg AM		36/791 (4.6%)	45/802 (5.6%)	47/793 (5.9%)
Change from Baseline ≥ 10 mmHg PM		48/789 (6.1%)	44/802 (5.5%)	59/793 (7.4%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg AM		109/741 (14.7%)	122/741 (16.5%)	125/736 (17.0%)
Change from Baseline ≥ 5 mmHg PM		112/741 (15.1%)	128/741 (17.3%)	150/736 (20.4%)
Change from Baseline ≥ 10 mmHg AM		18/741 (2.4%)	20/741 (2.7%)	30/736 (4.1%)
Change from Baseline ≥ 10 mmHg PM		27/741 (3.6%)	29/741 (3.9%)	32/736 (4.3%)
Change from Baseline ≥ 15 mmHg AM		2/741 (0.3%)	6/741 (0.8%)	5/736 (0.7%)
Change from Baseline ≥ 15 mmHg PM		7/741 (0.9%)	3/741 (0.4%)	7/736 (1.0%)
<i>Normotensive</i>		n=488	n=509	n=478
Final Visit	AM/PM Diastolic			
Change from Baseline ≥ 10 mmHg AM		21/474 (4.4%)	27/498 (5.4%)	25/469 (5.3%)
Change from Baseline ≥ 10 mmHg PM		27/474 (5.7%)	28/498 (5.6%)	30/469 (6.4%)
2 Consecutive Postbaseline Visits				
Change from Baseline ≥ 5 mmHg AM		66/439 (15.0%)	81/459 (17.6%)	75/434 (17.3%)
Change from Baseline ≥ 5 mmHg PM		64/439 (14.6%)	82/459 (17.9%)	86/434 (19.8%)

Change from Baseline \geq 10 mmHg AM	12/439 (2.7%)	14/459 (3.1%)	18/434 (4.1%)
Change from Baseline \geq 10 mmHg PM	14/439 (3.2%)	16/459 (3.5%)	20/434 (4.6%)
Change from Baseline \geq 15 mmHg AM	0	5/459 (1.1%)	2/434 (0.5%)
Change from Baseline \geq 15 mmHg PM	3/439 (0.7%)	2/459 (0.4%)	1/434 (0.2%)
Hypertensive	n=324	n=311	n=334
Final Visit	AM/PM Diastolic		
Change from Baseline \geq 10 mmHg AM	15/317 (4.7%)	18/304 (5.9%)	15/317 (4.7%)
Change from Baseline \geq 10 mmHg PM	21/315 (6.7%)	16/304 (5.3%)	29/324 (9.0%)
2 Consecutive Postbaseline Visits			
Change from Baseline \geq 5 mmHg AM	75/434 (17.3%)	41/282 (14.5%)	50/302 (16.6%)
Change from Baseline \geq 5 mmHg PM	48/302 (15.9%)	46/282 (16.3%)	64/302 (21.2%)
Change from Baseline \geq 10 mmHg AM	18/434 (4.1%)	6/282 (2.1%)	12/302 (4.0%)
Change from Baseline \geq 10 mmHg PM	13/302 (4.3%)	13/282 (4.6%)	12/302 (4.0%)
Change from Baseline \geq 15 mmHg AM	2/434 (0.5%)	1/282 (0.4%)	3/302 (1.0%)
Change from Baseline \geq 15 mmHg PM	4/302 (1.3%)	1/282 (0.4%)	6/302 (2.0%)

Source: Tables 63 and 64, Study Report 178-CL-049, pages 217 and 218

Three mirabegron patients met the criterion for a PCS change in AM or PM DBP at any visit as measured by patient diary (\geq 105 mm Hg and \geq 15 mm Hg increase from baseline to Final Visit), 2 in the mirabegron 50 mg group and one in the 100 mg group. Seven (7) patients in the tolterodine ER 4 mg group met this criterion. One patient in the mirabegron 50 mg and one patient in the mirabegron 100 mg group had a diastolic PCS at Final Visit. All of these mirabegron patients had increased diastolic blood pressures noted during the screening period.

No patient met the criteria for a PCS change from baseline to Final Visit or any visit in SBP (\geq 180 mm Hg and \geq 20 mm Hg increase from baseline) or DBP (\geq 105 mm Hg and $>$ 15 mm Hg increase from baseline). There was 1 patient in each mirabegron dose groups who met the PCS systolic criteria at some point during the study. Both had pre-existing hypertension. There were three tolterodine subjects who met PCS criteria at some point during the study.

The table below provides changes from baseline in blood pressure between groups broken out by selected subsets (age, baseline BP, gender, combinations of these factors, etc).

Table 53: Selected Groups Adjusted Mean Change from Baseline to Final Visit in Blood Pressure Measured by Patient Diary

Parameter	Mean Change from Baseline (mmHg) (95% CI)					
	Mirabegron 50 mg		Mirabegron 100mg		Tolterodine ER 4 mg	
Group/Subgroup	n		n		n	
AM SBP						
Overall	791	0.2 (0.4, 0.9)	802	0.4 (-0.2, 1.1)	793	-0.5 (-1.1, 0.2)
Normotensive	474	0.3 (-0.4, 1.1)	498	1.0 (0.3, 1.7)	469	-0.3(-1.1, 0.4)
Male	205	1.7 (-1.0, 0.5)	204	1.9 (0.6, 3.2)	206	-1.0 (-1.7, -0.2)
Female	586	-0.3 (-1.0, 0.5)	598	-0.1 (-0.9, 0.6)	587	-1.0 (-1.7, -0.2)
Female ≥ 65 years	282	1.6 (0.5, 2.7)	309	1.8 (0.8, 2.9)	297	0.5 (-0.5, 1.6)
PM SBP						
Overall	789	-0.3 (-0.9, 0.3)	802	0.1 (-0.5, 0.8)	793	-0.0 (-0.7, 0.6)
Normotensive	474	-0.4 (-1.1, 0.4)	498	0.9 (0.2, 1.6)	469	-0.0 (-0.8, 0.7)
Male	204	1.9 (0.6, 3.2)	204	1.5 (0.3, 2.8)	206	1.2 (-0.1, 2.4)
Female ≥ 65 years	282	0.5 (-0.6, 1.6)	309	1.1 (0.1, 2.1)	287	0.6 (-0.5, 1.6)
AM DBP						
Overall	791	-0.3 (-0.7, 0.1)	802	0.4 (-0.0, 0.8)	793	0.1 (-0.3, 0.5)
Normotensive	474	-0.2 (-0.7, 0.3)	498	0.8 (0.3, 1.3)	469	0.2 (-0.3, 0.7)
Male	205	-0.2 (-1.0, 0.6)	204	0.9 (0.1, 1.7)	206	0.3 (-0.5, 1.1)
Female < 65 years	509	-0.3 (-0.8, 0.2)	493	0.8 (0.3, 1.4)	496	0.4 (-0.1, 0.9)
PM DBP						
Overall	789	-0.0 (-0.4, 0.4)	802	0.1 (-0.3, 0.5)	793	0.6 (0.2, 1.0)
Hypertensive	315	-0.2 (-0.9, 0.5)	304	-0.3 (-1.0, 0.4)	324	0.9 (0.2, 1.6)
Female	585	-0.2 (-0.7, 0.3)	598	-0.1 (-0.5, 0.4)	587	0.6 (0.1, 1.1)
Female < 65 years	507	0.3 (-0.2, 0.8)	493	0.7 (0.2, 1.2)	496	1.1 (0.6, 1.6)

Bold text indicates an increase from baseline for which the 95% CI excludes zero.

Source: Table 69, Study Report 178-CL-049, page 225

Reviewer's Comment: In this study, men appeared to have a greater propensity to increase in BP related to mirabegron compared to women.

ECGs

The percentage of patients with a normal ECG assessment at baseline and an abnormal assessment at month 6 was 9.5%, 9.9% and 10.4% in the mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg groups, respectively. The percentage of patients with a normal ECG assessment at baseline and an abnormal assessment at the Final Visit was slightly higher (but comparable) in the mirabegron 100 mg and tolterodine ER 4 mg treatment groups (10.6% and 11.1%, respectively) compared with the mirabegron 50 mg treatment group (8.3%).

QTcF absolute values > 500 msec at any time during the study were observed for 2 patients (0.3%) in the mirabegron 50 mg group, 1 patient (0.1%) in the mirabegron 100 mg group and 1 patient (0.1%) in the tolterodine ER 4 mg group. Of these patients, 3 had a baseline QTcF value > 500 msec and one had a baseline value of 495 msec. None of these patients had a TEAE of QTc interval prolongation reported. The incidence of QTcF absolute values > 480 msec and > 450 msec was slightly higher (but comparable) in the mirabegron 50 mg (0.7% and 4.9%, respectively) and tolterodine ER 4 mg (0.8% and 4.4%, respectively) treatment groups compared with the mirabegron 100 mg treatment group (0.3% and 3.9%, respectively).

Ten patients, 3 each in the mirabegron 50 mg and 100 mg groups and 4 in the tolterodine ER 4 mg group, had ≥ 60 msec increases in QTcF. With the exception of 1 patient in the tolterodine ER 4 mg group (Patient No. 3026-1649: cardiac arrest; this event was adjudicated as ventricular fibrillation), no TEAEs in the Torsade de Pointes/QT prolongation SMQ occurred in patients who had ≥ 60 msec increases in QTcF.

Treatment-emergent sinus tachycardia, defined by the central reader as mean heart rate > 100 bpm and mean PR not missing, was noted in 16 patients (7 patients in the mirabegron 50 mg group, 3 patients in the mirabegron 100 mg group and 6 patients in the tolterodine ER 4 mg group). Treatment-emergent atrial fibrillation was noted in 3 patients (2 patients in the mirabegron 100 mg group and 1 patient in the tolterodine ER 4 mg group).

In the mirabegron 50 mg and 100 mg treatment groups, mean increases in heart rate from baseline to Final Visit were numerically higher in females (1.3 bpm and 2.8 bpm, respectively) compared to males (0.7 bpm and 1.5 bpm, respectively). In the tolterodine ER 4 mg group, mean increases from baseline to Final Visit in heart rate were 3.1 bpm in both male and female patients, both of which are greater than what was observed in mirabegron treated patients. Mean increases from baseline to Final Visit in heart rate were generally similar in patients < 65 years of age compared to patients ≥ 65 years of age within each treatment group. By gender analyses of mean changes from baseline to Final Visit in QTcF represented a small (≤ 1.6 msec) mean increase in all cases except for female patients in the mirabegron 100 mg group where a small decrease was noted (-0.5 msec). Mean changes from baseline to Final Visit in QTcF were similar in both age groups within each treatment group. Patients < 65 years of age and patients ≥ 65 years of age had mean decreases from baseline to Final Visit in the mirabegron 100 mg group (-0.2 msec for both age groups), while the mirabegron 50 mg group and tolterodine ER 4 mg group showed small (≤ 1.7 msec) mean increases.

Overall Conclusions

A total of 2444 patients were evaluated for safety; of these, 81.3% of patients 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. OAB-related baseline characteristics were consistent across treatment groups.

The mean number of micturitions per 24 hours at baseline ranged from 10.94 to 11.16. The overall mean level of urgency was 2.44, and the mean number of urgency episodes (grade 3 or 4) was 5.57. A total of 1385 patients received mirabegron (either dose) for at least 6 months, and 564 patients received mirabegron for at least 1 year.

Both doses of mirabegron were effective, as assessed by changes-from baseline and comparisons to the active control, tolterodine LA, in treating these symptoms of OAB at month 1 (the first postdose assessment period) and efficacy was (numerically) maintained throughout the 12-month study. Both doses of mirabegron also showed numeric improvement on the additional secondary efficacy variables, including Symptom Bother, HRQL, treatment satisfaction, pad usage, number of nocturia episodes, PPBC, work productivity and health status. Tolterodine ER 4 mg was included in this study to put results into context with a commonly used treatment for OAB. Of note, 3.6% of mirabegron-treated patients in the SAF discontinued the study due to lack of efficacy compared to 5.5% of tolterodine ER 4 mg-treated patients.

A reduction in incontinence episodes per 24 hours was noted in all treatment groups. At month 1, the adjusted mean changes from baseline in mean number of incontinence episodes were -0.92, -1.00 and -0.95 for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively, and at month 12, these changes were -1.05, -1.23 and -1.33 for the same respective treatment groups.

A reduction in micturitions per 24 hours was noted in all treatment groups. At month 1, the adjusted mean changes from baseline in mean number of micturitions per 24 hours were -0.93, -1.09 and -1.01 for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, respectively, and at month 12, these changes were -1.30, -1.43 and -1.47 for the same respective treatment groups.

Treatment with mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg resulted in a numeric increase from baseline in mean volume voided per micturition at month 1 (12.1 mL, 16.7 mL and 16.0 mL respectively). In the mirabegron 50 and 100 mg treatment groups, mean volume voided continued to increase, at least modestly, over the course of the study to month 12 (adjusted mean change from baseline to month 12: 18.0 mL and 22.6 mL, respectively). In the tolterodine ER 4 mg group, the effect on mean volume voided at month 1 was generally maintained to month 12 (adjusted mean change from baseline to month 12: 18.4 mL).

A greater number of events within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) were reported in the mirabegron 100 mg treatment group as compared to the active comparator and the mirabegron 50 mg treatment group. The reported neoplasms were heterogeneous in tissue of origin. Upon analysis of these neoplasms, it is this reviewer's conclusion that the independent role of mirabegron 100 mg remains unclear, and a large, postmarketing epidemiology type study might be appropriate to clarify the role of mirabegron. An appropriate post marketing study/commitment is recommended.

When compared to tolterodine ER 4 mg, no consistent effect of mirabegron on mean SBP or DBP were observed based on changes from baseline to each visit and Final Visit. No overt trends were observed in blood pressure when assessed by normotensive and hypertensive populations or by sex or age. There were, however, several adverse event reports of worsened hypertension in patients taking mirabegron, and a single case of a very high blood pressure (240/120 mm Hg) in 1 patient taking mirabegron 100 mg.

For both doses of mirabegron examined in this study, the pulse rate increases observed are comparable to or less than pulse rate changes of the active comparator. Tachycardia (PT) occurred at a lower rate in mirabegron 50 mg and 100 mg treatment groups compared to tolterodine ER 4 mg (1.0%, 2.3% and 3.1%, respectively). No events of tachycardia resulted in permanent discontinuation of study drug. AM pulse rates changes observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg were 0.9 bpm, 1.6 bpm and 1.5 bpm, respectively and PM pulse rate changes observed for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg were 0.4 bpm, 1.3 bpm and 1.9 bpm, respectively.

There were more cardiac arrhythmia events in tolterodine-treated patients than in mirabegron-treated patients. No dose-dependent observations were apparent in the mirabegron treated-patients. Medically important cases of atrial fibrillation based upon criteria to assess new or worsening cases of treatment-emergent atrial fibrillation were comparable between treatment groups. The overall incidence of adjudicated APTC/MACE cardiovascular events was 0.7% in the mirabegron 50 mg group, none in the mirabegron 100 mg group and 0.5% in the tolterodine ER 4 mg group.

The Sponsor conducted search of events for hypersensitivity. 7 patients were identified with events of “likely hypersensitivity” where the study drug may have been a precipitating factor. This includes 3 patients in the mirabegron 50 mg group, 3 patients in the mirabegron 100 mg group and 1 patient in the tolterodine ER 4 mg group. There was one notable adverse event of urticaria and one notable adverse of pruritis/rash with a positive re-challenge, in mirabegron-treated patients.

Two patients, 1 in the mirabegron 50 mg group and 1 in the tolterodine ER 4 mg group, experienced syncope-type events (PT in both patients: loss of consciousness). The mirabegron-treated patient had a concomitant TEAE of pyrexia. No events of seizure were reported in the study.

Urinary retention was reported for 1 patient each in the mirabegron 50 mg and 100 mg groups and 3 patients in the tolterodine ER 4 mg group. Of these patients, acute urinary retention was reported for 1 patient (0.1%) in the mirabegron 100 mg group and 1 patient (0.1%) in the tolterodine ER 4 mg group.

One patient in the mirabegron 50 mg treatment group had concomitant elevations in ALT and/or AST > 3 times the ULN and total bilirubin > 2 times the ULN; however, this patient had ongoing hepatitis B and a past history of alcoholism that definitively rules out a case of Hy’s Law due to the alternate etiology of viral hepatitis. The overall incidence of hepatic disorders

events in the Possible Drug-related Hepatic Disorders SMQ was similar across treatment groups. There was one notable case of liver injury (with biopsy evidence) in a patient taking mirabegron 100 mg.

No consistent trends in ECG changes were identified. There was no evidence of increased incidence of QTc interval prolongation in mirabegron-treated patients.

Other than the potential neoplasm safety signal, a small number of cases of worsened hypertension, several allergic-type AEs, and one or two other AEs, the long term safety and tolerability of mirabegron at doses of 50 and 100mg has been characterized by this long-term safety study and shown to be generally acceptable and comparable to an established OAB treatment.

The following special clinical safety study will be discussed in brief:

Study 178-CL-060: A Phase 2, Double-Blind, Parallel Group, Placebo Controlled, Multi-Center Study to Evaluate the Urodynamics and Safety of YM178 in Male Subjects with Lower Tract Symptoms (LUTS) and Bladder Outlet Obstruction (BOO).

This 12 week study enrolled 200 patients (65 placebo, 70 mirabegron 50 mg and 65 mirabegron 100 mg). This special safety study was designed to investigate the effect of mirabegron on bladder emptying and to demonstrate the lack of a detrimental effect on bladder function in men with bladder outlet obstruction. Randomization ratio to study arm was 1:1:1. The double-blind treatment period was 12 weeks. The study included males at least 45 years of age with a diagnosis of LUTS and BOO, who had a BOO Index (BOOI) ≥ 20 , International Prostate Symptom Score (IPSS) ≥ 8 , maximum urine flow ≤ 12 mL/sec with a voided volume of ≥ 120 mL, and biochemistry and hematology laboratory test results of normal or abnormal not clinically significant. Patients were excluded who had a total daily urine volume > 3000 mL. The primary variables in this study were urodynamic safety variables maximum flow rate (Qmax) and detrusor pressure at maximum flow rate (PdetQmax). Secondary safety variables included urodynamic variables Bladder Contractile Index (BCI) and Bladder Voiding Efficiency (BVE), as well as Postvoid Residual Volume (PVR).

Reviewer's Comment: In other clinical trials testing for drug efficacy in treating BPH-LUTS, IPSS inclusion criteria was a score of ≥ 13 , but the flow rate could be as high as ≤ 15 . In this trial, symptoms could be mild, but flow rate was reduced. Also, in other studies the BOOI was not used as an inclusion criterion.

The Sponsor concludes that in this study, both the mirabegron 50 mg (change from baseline: -1.35; P=0.0215) and the mirabegron 100 mg (change from baseline: -1.37; P=0.0233) treatment groups were associated with significant improvements in mean number of micturitions per 24 hours compared with that for placebo (change from baseline: -0.31). The sample size of patients

with incontinence episodes was small (placebo n=9, mirabegron 50 mg n=18, and mirabegron 100 mg n=13). Neither mirabegron group had a significant reduction in incontinence episodes, but this may be due to the small sample of incontinent patients. There was no difference between either mirabegron treatment group and the placebo group for IPSS total scores. Both mirabegron treatment groups (changes from baseline; mirabegron 50 mg: 15.82 mL; mirabegron 100 mg: 15.80 mL) were associated with small numerical increases in mean volume per micturition at the end of treatment compared to that of the placebo group (change from baseline: 5.40 mL); however, these changes did not reach statistical significance.

Results from the primary analyses indicated that treatment with mirabegron 50 mg or 100 mg was non-inferior to placebo with respect to urinary flow and detrusor pressure at peak flow as neither mirabegron dose decreased Qmax by the pre-specified margin of 3 mL/second (the lower limits of the 95% CI were -0.63 for the mirabegron 50 mg group and -0.43 for the mirabegron 100 mg group) or increased PdetQmax by the pre-specified margin of 15 cmH₂O (the upper limits of the 95% CI were 2.09 for the mirabegron 50 mg group and 6.96 for the mirabegron 100 mg group).

More patients in the placebo group (10/63, 15.9%) than in the mirabegron 50 mg and 100 mg treatment groups (5/64, 7.8% and 4/58, 6.9%, respectively) shifted from a BOOI of 20-40 (equivocal) at baseline to a BOOI of > 40 (obstructed) at the end of treatment. There were no shifts from normal BOOI to obstructed at end of treatment in any treatment group. While there was an decrease in the BCI (Bladder Contractile Index) for mirabegron 50 as compared to placebo, this parameter improved in the 100 mg mirabegron dose as compared to placebo.

Although no overt trend in adjusted mean change from baseline in PVR volumes were observed at weeks 1, 4, and 8, a dose-dependent increase in PVR was observed at week 12 and end of treatment in mirabegron treated patients. This increase only reached statistical significance (P=0.0459) at the end of treatment in the 100 mg mirabegron group (30.77 mL) compared with the placebo group (0.55 mL) for patients who received at least one dose of the study drug(SAF).

Two patients in the study experienced an adverse event of urinary retention (Patient No. 18335201 in the placebo group on day 84 and Patient No. 18175255 in the mirabegron 100 mg group on day 45). Both episodes of urinary retention lasted approximately 1 day and resolved without invasive intervention (abdominal palpation) in the patient who received mirabegron 100 mg, but required catheterization in the patient who received placebo. A narrative is provided below only for the mirabegron patient:

Subject 18175255: Temporary Urinary Retention: The subject is a 60 year old white US male randomized to mirabegron 100 mg on 9 October 2007. The patient had been using alfuzosin from Days -862 to -29. On Day one the subject's IPSS Total score was 21 and his voided volumes ranged from 50 to 225 mL. On day 45, an adverse event of temporary urinary retention was reported. The subject presented to the clinic with a complaint of not being able to urinate for approximately 12 hours. The subject's abdomen was palpated and a PVR ultrasound

noted 450cc of urine in the bladder. The subject's abdomen was soft and there were no complaints of pain upon palpitation. After drinking several glasses of water, the subject was able to void within 2 hours of the ultrasound. The subject had an adverse event of an urge to urinate for several minutes after urinating from day 36 through day 37. The patient's PVRs at screening, Day 1, Day 8, Day 38, Day 45, Day 66 and Day 94 were 44, 55, 31, 10, 450, 48 and 2 mL respectively.

The patient's micturitions per day increased from 12.0 at baseline and 11.3 at Week 4 to 15.7 at Week 8, but by Week 12 they were 8.0. His episodes of urgency per day increased from 1.3 at baseline and 2.0 at Week 4 to 5.0 at Week 8 but at Week 12 were 0.7 (Appendix Table 13.2.6.3.2).

Reviewer's Comment: Since the patient had a negative rechallenge (94 days on study drug), I cannot attribute causality to mirabegron.

Reviewer's Safety Conclusions: Mirabegron at 50 mg and 100 mg daily did not adversely affect measures of detrusor function: i. e. detrusor pressure at maximum flow rate or the maximum flow rate in male BPH subjects. Derived measures of outflow obstruction also were not adversely affected. The potential for urinary retention in males with BPH was low in this study. This study does not include sufficient number of subjects or a long enough duration of treatment to justify special labeling for safety in patients with bladder outlet obstruction. At the time same, it raises no particular concern and provides some degree of comfort in the event of use in men with latent BOO.

6 Review of Efficacy

Efficacy Summary

The co-primary efficacy endpoints in the pivotal analysis set (Studies 178-CL-046, 178-CL-047 and 178-CL-074) were the change from baseline to endpoint in the mean number of incontinence episodes per 24 hours as compared to placebo and the mean change from baseline to endpoint in the mean number of micturitions per 24 hours as compared to placebo. Treatment with mirabegron 50 mg and 25 mg in the pooled efficacy analysis resulted in a reduction of incontinence episodes per 24 hours at Week 12 as compared to placebo of -0.40 ($p < 0.001$ corrected for multiplicity) and for 25 mg -0.40 ($p = 0.005$ adjusted for multiplicity). Treatment with mirabegron 50 mg and 25 mg in the pooled efficacy analysis resulted in a reduction of micturitions per 24 hours at Week 12 as compared to placebo of -0.75 ($p < 0.001$ corrected for multiplicity) and for 25 mg -0.47 ($p = 0.007$ adjusted for multiplicity). In each of the individual studies, the co-primary endpoints also achieved changes as compared to placebo at endpoint that were statistically and clinically significant. The 95% 2-sided confidence intervals for adjusted mean change from baseline as compared to placebo with respect to daily number of micturitions and daily incontinence episodes for mirabegron 50 mg do not overlap. For the 25 mg mirabegron dose there is minimal overlap for these confidence limits possibly reflecting the smaller number of patients receiving 25 mg in the phase 3 program. It is

reasonable to conclude that both 25 mg and 50 mg are effective doses for the primary endpoints, although 50 mg appears modestly more effective.

The secondary endpoint of change from baseline to endpoint in mean voided volume in the pooled primary studies was as expressed as adjusted difference versus placebo was 11.9 cc ($p < 0.001$ adjusted for multiplicity) for mirabegron 50 mg. Mirabegron 25 mg resulted in a mean change from placebo of 4.6 cc ($p 0.15$) which was not statistically significant.

(b) (4)

At 4 weeks, mirabegron 50 mg demonstrated a significantly decreased number of incontinence episodes for 24 hours as compared to placebo as well as a significantly decreased number of micturitions for 24 hours as compared to placebo. For mirabegron 25 mg, significant decreases in number of incontinence episodes and daily micturitions were not seen until 8 weeks. At 8 weeks, however, the observed benefit of 25 mg and 50 mg appears comparable.

While there are minor efficacy differences noted between mirabegron 25 mg and 50 mg in secondary endpoints and time to onset of statistically significant primary efficacy endpoint changes, in light of some of the adverse events noted for mirabegron and their relation to increased drug exposure, some Advisory Committee members have recommended starting all patients at mirabegron 25mg daily. Those subjects who achieve a satisfactory response to mirabegron 25 mg may therefore have less risk for adverse events as such may reduce risk for the entire mirabegron population. Based on the evidence, this is a reasonable plan for dosing.

In the 1 year active controlled safety study (049), mirabegron 50 mg maintained efficacy over the course of the study period as assessed by the co-primary endpoints.

Both mirabegron 25 mg and 50 mg were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours from baseline to final visit for both male and female patients. A larger reduction versus placebo in mean number of incontinence episodes was observed in female patients compared to male patients. This could reflect a lower baseline level of incontinence in males and overlapping symptomatology with male comorbid conditions as well as the increased female mirabegron exposure.

The reduction from baseline to final visit in mean number of incontinence episodes per 24 hours (adjusted mean versus placebo) was lower within the <65 years of age group for mirabegron 50 mg (-0.22) as compared with the ≥ 65 years of age group (-0.66). There was a similar finding for mirabegron 25 mg with the values being -0.29 for under < 65 years and 0.59 for ≥ 65 years of age. With respect to mean number of micturitions per 24 hours, there also appears to improved efficacy in the over 65 year age group not reaching statistical significance. It does appear that overall, there is increased efficacy in patients > 65 years of age as compared to patients <65 years of age.

In efficacy analyses by geographic region, both mirabegron 25 mg and 50 mg were efficacious in reducing mean number of incontinence episodes and micturitions per 24 hours. There was

a higher placebo effect noted in patients in North America making the effect size less in these subjects.

In the subpopulation analysis of patients by race, there were too few patients in categories other than white to allow confidence limits that did not include 0.

The interaction by subgroup p-value for efficacy based on BMI did not reach significant levels ($p < 0.05$) for any BMI subgroup.

Efficacy in diabetics and patients on beta-blockers were comparable to the general OAB study population.

With respect to concomitant alpha-blocker use, mirabegron 50 mg reduced the daily incidence of incontinence episodes, but well below that in the overall study population (-0.12 versus -0.55). For mirabegron 100, the converse is true. The numbers of patients using alpha-blockers may be too small to draw meaningful conclusions.

Mirabegron 50 and 100 mg did not demonstrate benefit in terms of decreasing the mean number of incontinence episodes in men with BPH. The 50 mg mirabegron dose only modestly decreased micturition episodes in men with BPH. There are too few men with BPH included in the pivotal studies to draw meaningful conclusions.

In patients with concomitant diuretic use, the efficacy of both mirabegron 50 mg and 100 mg was superior to the efficacy of patients not on diuretic use and exceeded the efficacy results in the overall study population for the primary efficacy endpoints.

There are no efficacy findings or findings from subgroup analysis that should change the Sponsor's dosing recommendations.

The starting dose for mirabegron, in my opinion, should be mirabegron 25 mg once daily for all patients, with upward titration for those subjects who do not achieve satisfactory clinical improvement at 8 weeks.

6.1 Indication

Mirabegron is a beta 3-adrenoceptor agonist indicated for the treatment of over active bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

6.1.1 Methods

The methods employed for each Pivotal study and the Long-term, active-controlled safety study have been discussed in detail in Section 5.3.

6.1.2 Demographics

The individual studies are discussed in Section 5.3.

Populations in the mirabegron development program for OAB are reflective of the population that would receive the product after market approval. Inclusion and exclusion criteria in the phase 3 studies were sufficiently broad to allow inclusion of patients who were OAB anti-muscarinic treatment naive as well as patients who received prior OAB anti-muscarinic therapy. Patients in the primary phase 3 studies (safety analysis set [SAF]) were predominantly female (approximately 72%) and White (approximately 94%) with a mean age of 59 years (range 18-95 years). Approximately 38% of patients were ≥ 65 years of age and approximately 12% of patients were ≥ 75 years of age across the treatment groups.

At baseline, patients in the FAS had a mean of 11.6 micturitions per 24 hours. Of those patients with incontinence at baseline, the mean number of incontinence episodes was 1.8 episodes per 24 hours. All three types of OAB were represented, including urge incontinence only, mixed stress/urge incontinence with urge as predominant factor, and frequency/urgency without incontinence. Mean duration of OAB symptoms was similar across treatment groups in the FAS, ranging from 85.2 to 88.3 months. The proportion of FAS patients with prior surgery for OAB was relatively consistent across treatment groups, ranging from 8.3% to 9.5%. Approximately 52% of patients received prior anti-muscarinic OAB medications; of these patients, 66% of patients discontinued prior anti-muscarinic OAB medication due to lack of effect and 25% discontinued due to poor tolerability.

Demographics and OAB characteristics of the population enrolled were generally similar across the primary phase 3 studies.

Table 54: Summary Patient Demographics Phase 3 Placebo-Controlled Studies 178-CL-046, 178-CL-047 and 178-CL-074

Category	178-CL-046		178-CL-047		178-CL-074	
n(%)	FAS	FAS-I	FAS	FAS-I	FAS	FAS-I
	n=1906	n=1165	n=1270	n=993	n=1251	n=773
Gender						
Male	534 (28.0%)	193 (16.6%)	320 (25.2%)	168 (18.0%)	394 (31.5%)	158 (20.4%)
Female	1372 (72.0%)	972 (83.4%)	950 (74.8%)	765 (82.0%)	857 (68.5%)	615 (79.6%)
Age mean (SD)	59.1 (12.43)	60.0 (12.13)	60.2 (13.37)	61.1 (13.31)	59.1 (12.96)	60.0 (12.59)
Race						
White	1891 (99.2%)	1153 (99.0%)	1120 (88.2%)	830 (89.0%)	1134 (90.6%)	696 (90.0%)
Black	6 (0.3%)	5 (0.4%)	108 (8.5%)	78 (8.4%)	96 (7.7%)	65 (8.4%)
Asian	5 (0.3%)	4 (0.3%)	23 (1.8%)	11 (1.2%)	16 (1.3%)	10 (1.3%)
Other	4 (0.2%)	3 (0.3%)	19 (1.5%)	14 (1.5%)	5 (0.4%)	2 (0.3%)
BMI (kg/m ²)						

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<25	592 (31.1%)	332 (28.5%)	307 (24.2%)	216 (23.2%)	317 (25.3%)	181 (23.4%)
25-<30	765 (40.2%)	449 (38.5%)	421 (33.2%)	297 (31.8%)	466 (37.3%)	277 (35.8%)
≥30	548 (28.8%)	384 (33.0%)	541 (42.6%)	420 (45.0%)	468 (37.4%)	315 (40.8%)
Geographical Region						
Eastern Europe	873 (45.8%)	507 (43.5%)			222 (17.7%)	115 (14.9%)
Western Europe	1033(54.2%)*	658 (56.5%)*			359 (28.7%)	219 (28.3%)
Northeastern US			224 (17.6%)	153 (16.4%)	118 (9.4%)	83 (10.7%)
Midwestern US			161 (12.7%)	114 (12.2%)	68 (5.4%)	42 (5.4%)
Southern US			429 (33.8%)	325 (34.8%)	209 (16.7%)	142 (18.4%)
Western US			329 (25.9%)	247 (26.5%)	189 (15.1%)	121 (15.7%)
Canada			127 (10.0%)	94 (10.1%)	86 (6.9%)	51 (6.6%)

* includes Australia

Source: Table 2, Summary of Clinical Efficacy (NDA submission), page 20.

6.1.3 Subject Disposition

For Study 178-CL-046, a total of 2437 patients were screened, 2397 patients entered the placebo run-in period, 2336 patients received placebo run-in study drug, and 1987 patients were randomized into the study. A total of 9 patients that were randomized did not receive double-blind study drug and were not included in the FAS or the safety analysis set (SAF). The proportion of patients randomized into the double-blind treatment period that discontinued the study (8.9% to 11.5%) was comparable across treatment groups. In each treatment group, the 2 most frequently cited reasons for discontinuation were adverse events (AEs) (2.6% to 5.0%) and consent withdrawal (1.8% to 3.4%). Overall, 95.9% (1906/1987) of randomized patients were included in the FAS. Overall, 58.6% (1165/1987) of randomized patients were included in the FAS-I, which was comprised of patients in the FAS who had at least one incontinence episode in the baseline diary.

For Study 178-CL-047, a total of 2342 patients were screened, 2306 patients entered the placebo run-in period, 2149 patients took placebo run-in study drug, and 1329 patients were randomized into the study and 1328 received double-blind study medication (SAF population). The proportion of patients randomized into the double-blind treatment period that discontinued the study was comparable across treatment groups (12.2% to 15.2%). In each treatment group, the 2 most frequently cited primary reasons for discontinuation were withdrawal of consent (3.7% to 6.4%) and AEs (3.7% to 4.4%). Overall, 95.6% (1270/1329) of randomized patients were included in the FAS and 70.2% (933/1329) were included in the FAS-I.

For Study 178-CL-074, a total of 2201 patients were screened, 2060 patients entered the placebo run-in period, 2030 patients took placebo run-in study drug, 1306 patients were randomized into the study, and 1305 patients received study drug. The proportion of patients randomized into the double-blind treatment period that discontinued the study was comparable across treatment groups (10.6% to 15.2%). In each treatment group, the 2 most frequently cited primary reasons for discontinuation were withdrawal of consent (2.8% to 4.6%) and AEs (2.7% to 3.9%). Overall, 95.8% (1251/1306) of randomized patients were included in the FAS and 59.2% (773/1306) were included in the FAS-I.

For flow diagrams and discussion of disposition, the reader is referred to the individual study reviews.

6.1.4 Analysis of Primary Endpoint(s)

Table 55: Change From Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours, Pooled Primary Studies

	Placebo (n=878)	Mirabegron 25 mg (n=254)	Mirabegron 50 mg (n=862)	Mirabegron 100 mg (n=577)
Baseline				
Mean (SE)	2.73 (0.090)	2.65 (0.160)	2.71 (0.089)	2.79 (0.102)
Final Visit				
Mean (SE)	1.64 (0.087)	1.21 (0.131)	1.23 (0.076)	1.25 (0.093)
Change From Baseline				
Mean (SE)	-1.09 (0.085)	-1.36 (0.145)	-1.48 (0.078)	-1.54 (0.091)
Adjusted Difference vs Placebo				
Mean (SE)		-0.40 (0.17)	-0.40 (0.094)	-0.41 (0.110)
95% 2-sided CI			(-0.58, -0.21)	(-0.62, -0.19)
P value		0.005#	<0.001#	<0.001#
P values are nominal from paired comparisons vs placebo within stratified rank ANCOVA model				
# statistically significant superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only. The results for mirabegron 50 mg and 100 mg are pooled.				

Sources: Table 38, Integrated Summary of Efficacy, page 143; Table 17, 178-CL-074 Study Report, page 105.

Table 56: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours, Pooled Primary Studies

	Placebo (n=1328)	Mirabegron 25 mg (n=415)	Mirabegron 50 mg (n=1324)	Mirabegron 100 mg (n=890)
Baseline				
Mean (SE)	11.58 (0.085)	11.68 (0.153)	11.70 (0.088)	11.58 (0.012)
Final Visit				
Mean (SE)	10.39 (0.091)	10.02 (0.175)	9.93 (0.092)	9.83 (0.019)
Change From Baseline				
Mean (SE)	-1.18 (0.076)	-1.66 (0.145)	-1.77 (0.075)	-1.75 (0.094)
Adjusted Difference vs Placebo				
Mean (SE)		-0.47 (0.176)	-0.55 (0.099)	-0.54 (0.115)
95% 2-sided CI			(-0.75, -0.36)	(-0.77, -0.31)
P value		0.007#	<0.001#	<0.001#
P values are nominal from paired comparisons vs placebo within stratified rank ANCOVA model				
# statistically significant superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only. The results from mirabegron 50 mg and 100 mg are pooled..				

Sources: Table 39, Integrated Summary of Efficacy, page 147; Table 18, 178-CL-074 Study Report, page 106.

6.1.5 Analysis of Secondary Endpoints(s)

With respect to mirabegron 50 and 100 mg doses, the mean volume voided per micturition at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were 9.4, 21.4 and 21.7 mL for the placebo, mirabegron 50 mg and 100 mg groups, respectively. The adjusted mean differences versus placebo were 11.9 mL (mirabegron 50 mg) and 12.3 mL (mirabegron 100 mg). Mirabegron 50 and 100 mg groups demonstrated a statistically significant increase from baseline to final visit in mean volume voided per micturition compared with placebo with multiplicity adjustment. In repeated measures analysis, change from baseline to week 12 in mean volume voided per micturition demonstrated adjusted mean differences versus placebo of 12.6 mL for both the mirabegron 50 and 100 mg treatment groups. The mirabegron 25 mg group, evaluated only in Study 074, did not achieve a statistically significant change in mean volume voided.

Table 57: Change from Baseline to Final Visit in Mean Volume Voided (mL) per Micturition, Pooled Primary Studies

	Placebo (n=1328)	Mirabegron 25 mg (n=410)	Mirabegron 50 mg (n=1324)	Mirabegron 100 mg (n=890)
Baseline				
Mean (SE)	159.2 (1.54)	165 (2.84)	159.0 (1.55)	157.9 (1.89)
Final Visit				
Mean (SE)	168.6 (1.90)	177.6 (3.30)	180.2 (2.01)	179.9 (2.39)
Change From Baseline				
Mean (SE)	9.4 (1.31)	12.5 (2.23)	21.2 (1.31)	22.0 (1.52)
Adjusted Difference vs Placebo				
Mean (SE)		4.6 (3.16)	11.9 (1.82)	12.3 (2.12)
95% 2-sided CI		(-1.6, 10.8)	(8.3, 15.5)	(8.1, 16.5)
P value		0.15	< 0.001#	< 0.001#
P values are nominal from paired comparisons vs placebo within stratified rank ANCOVA model				
# statistically significant superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only. Results from mirabegron 50 mg and 100 mg are pooled.				

Sources: Table 20, 178-CL-074, page 111; Table 40, ISE, page 151.

Reviewer's Comment: Pooled data is presented here for the co-primary efficacy variables, as it gives a good overview of mirabegron efficacy at all doses. All mirabegron doses in each of three pivotal studies were clinically and statistically superior to placebo for the co-primary endpoints. The efficacy of the 25 mg mirabegron dose was tested only in Study 178-CL-074. For efficacy of each dose in comparison to placebo, the reader is referred to the efficacy tables in the individual pivotal study reviews. Efficacy data from individual studies, not pooled efficacy data, will be used in labeling. The to be marketed doses will be mirabegron 25 mg and mirabegron 50 mg.

Both mirabegron 50 and 100 mg demonstrated statistically significantly superior 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).

Mirabegron 50 mg and 100 mg groups demonstrated statistically significant reductions from baseline to Week 4 in mean number of incontinence episodes per 24 hours compared with placebo with multiplicity adjustment. The 25 mg mirabegron dose achieved statistically significant differences from placebo at Week 8, comparable to those achieved with mirabegron 50 mg.

Table 58: Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hours, Pooled Primary Studies

	Placebo (n=878)	Mirabegron 50 mg (n=862)	Mirabegron 100 mg (n=577)
Baseline			
Mean (SE)	2.73 (0.090)	2.71 (0.089)	2.79 (0.102)
Week 4			
Mean (SE)	2.06 (0.095)	1.59 (0.084)	1.69 (0.096)
Change From Baseline			
Mean (SE)	-0.67 (0.083)	-1.12 (0.077)	-1.10 (0.092)
Adjusted Difference vs Placebo			
Mean (SE)		-0.45 (0.099)	-0.42 (0.115)
95% 2-sided CI		(-0.64,-0.26)	(-0.65,-0.20)
P value		< 0.001#	< 0.001#
# statistically significant superior compared with placebo at the 0.05 level with multiplicity adjustment			

Source: Table 41, ISE, page 153

Reviewer's Comment: For efficacy of each dose in comparison to placebo, the reader is referred to the efficacy tables in the individual pivotal study reviews. It is these efficacy results that will be used in labeling and not the pooled data.

For the mean number of micturitions, the adjusted mean changes from baseline to Week 4 (the first measured time point) were -0.77, -1.17 and -1.33 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The adjusted mean differences versus placebo were -0.40 (mirabegron 50 mg) and -0.56 (mirabegron 100 mg). Each mirabegron group (50 mg and 100 mg) demonstrated a statistically significant reduction from baseline to Week 4 in mean number of micturitions per 24 hours compared with placebo with multiplicity adjustment.

Table 59: Change from Baseline to Week 4 in Mean Number of Micturitions per 24 hours, Pooled Primary Studies

	Placebo (n=1328)	Mirabegron 50 mg (n=1324)	Mirabegron 100 mg (n=890)
Baseline			
Mean (SE)	11.58 (0.085)	11.71 (0.089)	11.58 (0.102)
Week 4			
Mean (SE)	10.82 (0.092)	10.52 (0.097)	10.26 (0.107)
Change From Baseline			

Mean (SE)	-0.76 (0.068)	-1.19 (0.072)	-1.32 (0.085)
Adjusted Difference vs Placebo			
Mean (SE)		-0.40 (0.094)	-0.56 (0.110)
95% 2-sided CI		(-0.59,-0.22)	(-0.78,-0.35)
P value		< 0.001#	< 0.001#
# statistically significant superior compared with placebo at the 0.05 level with multiplicity adjustment			

Source: Table 42, ISE, page 154.

Reviewer's Comment: For efficacy of each dose in comparison to placebo, the reader is referred to the efficacy tables in the individual pivotal study reviews. It is these efficacy results that will be used in labeling and not the pooled data.

6.1.6 Other Endpoints

Other endpoints are briefly discussed to better inform the clinical significance of the primary and secondary endpoints included in the gated statistical analysis.

The mean number of urge incontinence episodes at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.98, -1.38 and -1.38 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively, using pooled data. The adjusted mean differences versus placebo were -0.40 (mirabegron 50 mg) and -0.40 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of urge incontinence episodes compared with placebo.

The mean number of severe urgency episodes (defined as Grade 3 or 4 [with Grade 4 representing an urge incontinence episode]) per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. Severe urgency Grade 3 is defined (based on PIPIUS page 16 of the SAP, ISE/SCE)) as "I could not postpone voiding, but had to rush to the toilet in order not to wet myself." The adjusted mean changes from baseline to final visit were -1.29, -1.93 and -1.89 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively using pooled data. The adjusted mean differences versus placebo were -0.64 (mirabegron 50 mg) and -0.60 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant difference in reduction from baseline to final visit in mean number of urgency episodes per 24 hours compared with placebo with multiplicity adjustment.

In the primary studies, nocturia was defined as waking at night one or more times to void (i.e., any voiding associated with sleep disturbance between the time the patient goes to bed with the intention to sleep until the time the patient gets up in the morning with the intention to stay awake). The mean number of nocturia episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. The adjusted mean changes from baseline to final visit were -0.42, -0.55 and -0.54 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively using pooled data. The adjusted mean differences versus placebo were -0.14

(mirabegron 50 mg) and -0.12 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant reduction from baseline to final visit in mean number of nocturia episodes per 24 hours compared with placebo.

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). The criterion for a responder for zero incontinence episodes required that a patient had incontinence episode(s) at baseline and zero incontinence episodes at final visit based on the 3-day micturition diary. At the final visit, the percentage of responders was 37.8%, 44.1% and 46.4% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively using pooled data. The difference versus placebo was 6.3% for the mirabegron 50 mg group and 8.6% for the mirabegron 100 mg group. The corresponding odds ratios for the mirabegron 50 and 100 mg groups were 1.32 and 1.58, respectively; statistical significance was achieved in both groups for responders for zero incontinence episodes.

The criterion for a responder with $\geq 50\%$ reduction in incontinence episodes resulted in the percentage of responders of 59.6%, 69.5% and 70.5% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively using pooled data. The difference versus placebo was 9.9% (mirabegron 50 mg) and 11.0% (mirabegron 100 mg). The corresponding odds ratios for the mirabegron 50 and 100 mg groups were 1.54 and 1.64, respectively; statistical significance was achieved for both treatment groups for responders with a $\geq 50\%$ reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.

The criterion for a responder for ≤ 8 micturitions per 24 hours 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. In the post-hoc evaluation of responders for ≤ 8 micturitions per 24 hours, the percentage of responders at final visit was 24.6%, 31.6% and 34.0% in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The difference versus placebo was 7.0% (mirabegron 50 mg) and 9.4% (mirabegron 100 mg). The corresponding odds ratios for the mirabegron 50 and 100 mg groups were 1.57 and 1.69, respectively; statistical significance was achieved for both treatment groups for responders with ≤ 8 micturitions per 24 hours at final visit.

For the TS-VAS (Treatment Satisfaction- Visual Analogue Scale), patients were asked to rate their satisfaction with the treatment by placing a vertical mark on a line that runs from 0 (No, not at all) to 10 (Yes, completely). The mean TS-VAS score at baseline was comparable across all treatment groups. The adjusted mean changes from baseline to final visit were 1.25, 2.01 and 2.33 for the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively. The adjusted mean differences versus placebo were 0.76 (mirabegron 50 mg) and 1.08 (mirabegron 100 mg). Each mirabegron group demonstrated a statistically significant increase from baseline to final visit in TS-VAS score, a quantitative instrument to assess subjective improvement in patients with OAB, compared with placebo.

At 8 weeks, the adjusted mean difference versus placebo for mean number of micturitions per 24 hours for mirabegron 25 mg was -1.53 (p 0.017). At 8 weeks the adjusted mean difference

versus placebo for mean number of incontinence episodes per 24 hours for mirabegron 25 mg was -1.38 (p 0.036). The differences from baseline and from placebo observed for mirabegron 25 mg at 8 weeks were comparable to those observed for mirbaegron 50 mg.

Reviewer's Comment: Other endpoints are described because they assess aspects of OAB that are not assessed by the typical endpoints used in trial. Even though some of these endpoints are not validated as fit for purpose from a regulatory standpoint, they may help inform the clinical relevance of the primary and secondary endpoint results. Most of these other endpoints favor mirabegron 50 mg in terms of improving OAB symptoms. While mirabegron 25 mg did not meet efficacy endpoints at 4 weeks, it did at 8 weeks. The reader is referred to Tables 26 and 27 in the 1780-CL-074 study review. While some non-key secondary endpoints seem to favor mirabegron 50 mg over mirabegron 25 mg, in light of toxicities noted at increased doses of mirabegron (e.g., blood pressure), consideration should be given to starting patients on mirabegron 25 mg and titrating to 50 mg after 8 weeks. The patients who have a clinical response to mirabegron 25 mg and do not have to titrate upward, may reduce the overall risk of the total population taking mirabegron.

6.1.7 Subpopulations

Table 60: Summary of Patients With and Without Intrinsic/Extrinsic Factors at Baseline: Pooled Primary Studies, FAS and FAS-I (incontinent)

	Placebo		Mirabegron 50 mg		Mirabegron 100 mg	
	FAS	FAS-I	FAS	FAS-I	FAS	FAS-I
	n=1328	n=878	n=1324	n=862	n=890	n=577
History of BPH						
n	362	154	382	168	241	94
Yes	147(40.6%)	60 (39.0%)	142(37.2%)	56 (33.3%)	95 (39.4%)	36 (38.3%)
No	215(59.4%)	94 (61.0%)	240(62.8%)	112(66.7%)	146(60.6%)	58 (61.7%)
History of Diabetes						
Yes	105 (7.9%)	76 (8.7%)	115 (8.7%)	79 (9.2%)	75 (8.4%)	59(10.2%)
No	1223(92.1%)	802(91.3%)	1209(91.3%)	783(90.8%)	815(91.6%)	518(89.8%)
Renal Status CrCl						
n	1328	878	1323	861	890	577
>=90	467 (35.2%)	288(32.8%)	462 (34.9%)	280(32.5%)	316(35.5%)	191(33.1%)
60 to < 90	768 (57.8%)	525(59.8%)	751 (56.8%)	501(58.2%)	509(57.2%)	341(59.1%)
30 to < 60	93 (7.0%)	65 (7.4%)	110 (8.3%)	80 (9.3%)	63 (7.1%)	44 (7.6%)
< 30	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.2%)
Ongoing beta-Blocker Treatment						
Yes	206 (15.5%)	154(17.5%)	185 (14.0%)	127(14.7%)	156(17.5%)	102(17.7%)
No	1122(84.5%)	724(82.5%)	1139(86.0%)	735(85.3%)	734(82.5%)	475(82.3%)

Ongoing Diuretic Treatment						
Yes	211 (15.9%)	151(17.2%)	192 (14.5%)	141(16.4%)	143(16.1%)	103(17.9%)
No	1117(84.1%)	727(82.8%)	1132(85.5%)	721(83.6%)	747(83.9%)	474(82.1%)
Ongoing alpha-Agonist Treatment						
Yes	81 (6.1%)	35 (4.0%)	91 (6.9%)	44 (5.1%)	66 (7.4%)	28 (4.9%)
No	1247 (93.9%)	843 (96.0%)	1233 (93.1%)	818 (94.9%)	824 (92.6%)	549 (95.1%)

Source: Table 36, ISE, page 138

Reviewer's Comment: The above table provides perspective for the sub group analyses presented below.

Gender

Analyses of the subpopulations by each gender demonstrated that the mirabegron 50 and 100 mg groups showed numerically larger reductions from baseline to final visit in mean number of incontinence episodes per 24 hours versus placebo in female patients (adjusted mean difference from placebo: -0.47 and -0.47, mirabegron 50 and 100 mg groups, respectively) compared with male patients (adjusted mean difference from placebo: -0.07 and -0.11, mirabegron 50 and 100 mg groups, respectively). All point estimates were favorable for mirabegron in both male and female patients. Due to the small sample sizes for male patients in the FAS-I, the CIs were larger compared with those observed in female patients. It should be noted that baseline mean values for incontinence episodes were lower in male patients (2.12, 2.25 and 2.01 episodes per 24 hours in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively) as compared with baseline mean values for female patients (2.86, 2.83 and 2.94 episodes per 24 hours in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively).

Reviewer's Comment: Male patients were less likely than female patients to have incontinence at baseline and demonstrated a higher placebo mean adjusted change from baseline. The small numbers of males in the studies relative to females provide limited ability to demonstrate an appreciable reduction in incontinence in males.

For Study 178-CL-074, in the subpopulation analysis of gender, mirabegron 25 and 50 mg were both effective in reducing the mean number of incontinence episodes per 24 hours from baseline to final visit for both male and female patients; the treatment by gender interaction P value was < 0.15 (P = 0.13). For male patients, the adjusted mean difference versus placebo was numerically

higher in the mirabegron 25 mg group (-1.02) as compared with mirabegron 50 mg (-0.47) whereas in female patients the adjusted mean difference versus placebo was numerically lower for mirabegron 25 mg (-0.24) compared with mirabegron 50 mg (-0.42).

The baseline mean number of micturitions per 24 hours for male and female patients was similar across treatment groups. In the placebo, mirabegron 50 mg and mirabegron 100 mg groups, the adjusted mean change from baseline to final visit in male patients was -0.92, -1.29 and -1.62, respectively and the reduction in female patients was -1.31, -1.93 and -1.79, respectively. Among male patients, the adjusted mean difference versus placebo was -0.37 (95% CI: -0.74, -0.01) in the mirabegron 50 mg group and -0.70 (95% CI: -1.12, -0.28) in the mirabegron 100 mg group. Among female patients, the adjusted mean difference versus placebo was -0.62 (95% CI: -0.85, -0.39) in the mirabegron 50 mg group and -0.48 (95% CI: -0.74, 0.22) in the mirabegron 100 mg group.

For Study 178-CL-074, in the subpopulation analysis by gender, mirabegron 25 and 50 mg reduced the mean number of micturitions per 24 hours from baseline to final visit for both male and female patients. The treatment by gender interaction P value was ≥ 0.15 (P = 0.69).

Reviewer's Comment: The outcomes in male patients with OAB overall with regard to the co-primary endpoints are less favorable than in women with OAB. The Sponsor points out that men with OAB symptoms may have comorbid conditions such as BPH with over-lapping symptomatology.

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 (adjusted mean difference versus placebo: -0.22 and -0.22, respectively) as compared with the ≥ 65 years of age group for mirabegron 50 and 100 mg groups (adjusted mean difference versus placebo: -0.66 and -0.68, respectively). In the placebo group the reduction from baseline to final visit in mean number of incontinence episodes per 24 hours was numerically larger in the < 65 years of age group (adjusted mean change from baseline: -1.19) as compared with the ≥ 65 years of age group (adjusted mean change from baseline: -0.96).

For Study 178-CL-074, in the subpopulation analysis of patients by age group (< 65/ ≥ 65 and < 75/ ≥ 75 years), both mirabegron 25 and 50 mg groups had a reduction from baseline to final visit for adjusted mean difference versus placebo in mean number of incontinence episodes per 24 hours in all age groups; the treatment-by-age interaction P value was ≥ 0.15 for both age groups. In the <65 years of age subject the adjusted mean difference in incontinence episodes per 24 hours as compared to placebo was -0.29 for mirabegron 25 mg and -0.24 for mirabegron 50 mg. For patients ≥ 75 years of age, the adjusted mean difference in incontinence episodes per 24 hours as compared to placebo was -0.65 for mirabegron 25 mg and -0.76 for mirabegron 50 mg.

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. The treatment by age group interaction P value was ≥ 0.15 for both age groups ($P = 0.31$ for age group $< 65/\geq 65$ and $P = 0.79$ for age group $< 75/\geq 75$ years). The placebo adjusted reductions of micturitions per day by age groups are as follows: for patients < 65 years of age -0.51 for mirabegron 50 mg and -0.41 for mirabegron 100 mg; for patients ≥ 65 years of age, -0.62 for mirabegron 50 mg and -0.75 for mirabegron 100 mg; for patients ≥ 75 years of age -0.36 for mirabegron 50 mg and -0.34 for mirabegron 100 mg.

For Study 178-CL-074, in the subpopulation analysis of patients by age group, both mirabegron 25 and 50 mg groups had a reduction from baseline to final visit for adjusted mean difference versus placebo in mean number of micturitions per 24 hours for patients < 65 and ≥ 65 years and for patients < 75 and ≥ 75 years of age. The treatment-by-age interaction P value was ≥ 0.15 for both age groups. For patients < 65 years old mean reduction from baseline to final visit for adjusted mean difference versus placebo was -0.28 for mirabegron 25 mg and -0.27 for mirabegron 50 mg. For patients ≥ 65 years old mean reduction from baseline to final visit for adjusted mean difference versus placebo was -0.81 for mirabegron 25 mg and -0.68 for mirabegron 50 mg.

Reviewer's Comment: For daily episodes of incontinence, it appears that the older population subgroups have increased efficacy compared to the younger population. With respect to frequency of micturitions, the > 65 years of age subpopulation has improved efficacy as compared to the < 65 years of age subgroup.

Mirabegron was still effective, but less efficacious in the ≥ 75 years of age population, compared to the other age categories. This could possibly reflect additional comorbidities with aging. It does appear that, overall, there is increased efficacy in patients > 65 years of age as compared to patients < 65 years of age. This resolves a review issue noted in the 74 Day Letter.

Race

In the subpopulation analysis of patients by race, 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 Whites. There were too few patients in the categories "Asian" and "Other" to draw meaningful conclusions about these groups. Although the point estimates for both mirabegron groups in Blacks or African Americans ($n = 177$) and in Asians ($n = 38$), and the mirabegron 50 mg group in Other ($n = 27$), were > 0 , the 95% CIs (confidence intervals) around the point estimates included 0. All treatment groups in the 12-week primary efficacy studies demonstrated a decrease from baseline in mean number of micturitions per 24 hours. For Study 178-CL-074, there were too few non-White patients to draw meaningful conclusions.

Geographic Region

Analyses of the subpopulations from Europe and North America demonstrated that both mirabegron 50 and 100 mg groups were effective in reducing the mean number of incontinence episodes per 24 hours from baseline to final visit at both European and North American sites. For Study 178-CL-074, in the subpopulation analysis of patients from Europe or North America, both mirabegron 25 and 50 mg groups had a reduction from baseline to final visit for adjusted mean difference versus placebo in mean number of incontinence episodes per 24 hours.

Analyses of the subpopulations from Europe and North America demonstrated that 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 Study 178-CL-074, in the subpopulation analysis of patients from Europe or North America, both mirabegron 25 and 50 mg groups had a reduction from baseline to final visit for adjusted mean difference versus placebo in mean number of micturitions per 24 hours.

BPH

Table 61: BPH Pooled Pivotal Trial Efficacy Data

Sub-population and Category				24° Mean Number Incontinence Episodes			24° Mean Number Micturitions		
				Placebo	Mirabegron		Placebo	Mirabegron	
					50 mg	100mg		50 mg	100 mg
History Of BPH	Yes	Adjusted Change from Baseline	n	60	56	36	147	142	95
			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)
BPH	Yes	Adjusted Difference vs Placebo	Mean		0.14	0.03		-0.16	-0.87
BPH	No	Adjusted Change from Baseline	n	94	112	58	215	240	146
			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)
BPH	No	Adjusted Difference vs Placebo	Mean		-0.09	0.04		-0.48	-0.50

Source: Table 55, ISE, page 203

Reviewer's Comment: Mirabegron 50 and 100 mg did not appear effective in decreasing the mean number of incontinence episodes in men with BPH. The 50 mg mirabegron dose only modestly decreased micturition episodes in men with BPH. However, there are too few patients to draw meaningful conclusions about efficacy in men with BPH.

Diabetes

In diabetic patients, mirabegron 50 mg and 100 mg decreased daily incontinence episodes (adjusted difference versus placebo) by -0.38 and -0.41 respectively. In diabetic patients, mirabegron 50 mg and 100 mg decreased daily micturitions (adjusted difference versus placebo) by -0.78 and -0.83 respectively.

Reviewers Comment: These results are comparable if not better than the overall population. Nonetheless, there too few patients to draw meaningful conclusions about this group.

Renal Status

In patients with creatinine clearances ranging from 30 mL/min to ≥ 90 mL/min the results for both reduction in daily incontinence episodes and daily micturitions are comparable to the overall pooled study population.

Reviewer's Comment: Again, there too few patients to draw meaningful conclusions about efficacy of mirabegron in patients with creatinine clearances below 60 mL/min.

Ongoing Beta-Blocker Use

Table 62: Ongoing Beta-Blocker Use Pooled Pivotal Efficacy Data

Sub-population and Category				24° Mean Number Incontinence Episodes			24° Mean Number Micturitions		
				Placebo	Mirabegron		Placebo	Mirabegron	
					50 mg	100mg		50 mg	100 mg
Ongoing Beta Blocker Use	Yes	Adjusted Change from Baseline	n	154	127	102	206	185	156
			Mean (SE)	-1.11 (0.159)	-1.66 (0.175)	-1.46 (0.197)	-1.08 (0.178)	-1.59 (0.188)	-1.64 (0.026)
	Yes	Adjusted Difference vs Placebo	Mean		-0.55	-0.35		-0.51	-0.56
	No	Adjusted Change from Baseline	n	724	735	475	1122	1139	734
			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)
	No	Adjusted							

		Difference vs Placebo	Mean		-0.37	-0.42		-0.55	-0.54

Source: Table 55, ISE, page 203. This table includes pooled data from studies 178-CL-046, 178-CL-047 and 178-CL-074.

Reviewer's Comment: It appears that patients using beta-blockers have similar efficacy results compared to patients not on ongoing beta-blockade. Since patients using beta-blockers may have increased comorbidities, it is important to know that the risk benefit of mirabegron still appears favorable.

Concomitant Diuretic Use

In patients with concomitant diuretic use, the efficacy of both mirabegron 50 mg and 100 mg was superior to the efficacy to that of patients not on diuretic use and exceeded the efficacy results in the overall study population for the primary efficacy endpoints.

Concomitant Alpha-1-Antagonist Use (Males only)

Mirabegron 50 mg reduced the daily incidence of incontinence episodes similarly to the reduction in the overall study population. The reduction in the number of daily micturitions was well below that in the overall study population (-0.12 versus -0.55). For 100 mg dose of mirabegron the converse was true.

Reviewer's Comment: The numbers of subjects using alpha blockers may be too small to draw meaningful conclusions concerning efficacy of mirabegron in this subpopulation..

6.1.8 Analysis of Other Information Relevant to Dosing Recommendations

The effect of age, sex, genotype, CYP2D6, renal and hepatic impairment on the pharmacokinetics of mirabegron was studied in several single and multiple dose studies as shown below:

Age: 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) in Phase 1 studies. Similar results were obtained for the elderly population aged 65 years and above. However, population PK analysis of phase 2 and 3 data appears to indicate that age modestly affects 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 appears not necessary.

Sex: Mirabegron C_{max} and AUC_{tau} were approximately 40% to 50% higher, respectively, in females compared with males. The magnitude of the sex differences is attenuated with correction

for body weight. 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, by Sponsor, to a higher absolute bioavailability of mirabegron in females compared to males. No dose adjustment based on sex is recommended by Sponsor; the Sponsor states, and it is true, that the efficacy and safety of mirabegron at the proposed therapeutic dose have been demonstrated in both males and females with OAB.

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

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 and 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 subject with a body weight of 30 kg and approximately 17% lower in a subject 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). The Sponsor concludes given documented safety of mirabegron at a 100 mg dose (twice the proposed therapeutic dose), the effect of body weight on plasma exposure is considered not clinically significant. Dose adjustment based on body weight is not necessary in the Sponsor's opinion, and this reviewer agrees.

Pediatric: No pediatric study has been conducted with mirabegron in the submitted development program.

Genetic Polymorphism: Genetic polymorphism for the CYP2D6 isozyme has no clinically relevant impact on mirabegron exposure. Following a single 160 mg dose of mirabegron administered as the IR formulation, mean C_{max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC_{tau} was 8% and 12% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers, and mean C_{max} values were similar between the two phenotypes. In a pooled analysis across Phase 1 studies, there was considerable overlap in exposure between the different predicted phenotypes and subjects who were poor metabolizers of CYP2D6 demonstrated AUC values in the range of those observed in extensive metabolizers. The Sponsor observes that the absence of substantial differences in exposure between poor and extensive metabolizers of CYP2D6 is consistent with the multiple elimination pathways for mirabegron.

Renal Impairment: Volunteers with renal impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and weight. Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment

(estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m² as estimated using the Modification of Diet in Renal Disease [MDRD] 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 m²), 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 m²), mean C_{max} and AUC_{inf} values were 92% and 118% higher, respectively. Although these increases in mirabegron C_{max} and AUC_{inf} are less than achieved with doubling of the dose, the Sponsor recommends a reduction of the dose to 25 mg once daily in patients with severe renal impairment. No adjustment of the dose is being recommended in patients with mild to moderate renal impairment. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1.73 m², or creatinine clearance (CL_{cr}) < 15 mL/min, or patients requiring hemodialysis) and, therefore, is not recommended for use in this patient population in the Sponsor's opinion.

Hepatic Impairment: Volunteers with hepatic impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and body mass index (BMI). 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. Although the increase in mirabegron AUC_{inf} is less than achieved with doubling of the dose, the Sponsor recommends a reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment. No adjustment of the dose is required in patients with mild hepatic impairment. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, the Sponsor is not recommended mirabegron for use in this patient population.

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. As mirabegron administration in the phase 2b and 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. Patients with OAB are considered otherwise healthy (unless age-related and other disease conditions are prevalent), and therefore a significant difference in PK characteristics of mirabegron between patients and healthy volunteers is not expected.

The effects of Extrinsic factors on mirabegron pharmacokinetics are discussed below:

Food: The effect of food or co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs were studied in several single and multiple dose studies. Co-administration of a 50 mg tablet 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 without regard to food and these studies demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose according to the Sponsor, and as agreed upon by Clinical Pharmacology. These findings are discussed extensively in a Research Report: Mirabegron and Food Effect in this NDA submission.

Effect of Co-administered Drugs: Mirabegron is cleared by multiple mechanisms (metabolism, renal and possibly biliary excretion) and drug-metabolizing enzymes, with no single predominating clearance pathway. Therefore, co-administered drugs were expected to have a low propensity to affect the pharmacokinetics of mirabegron. These expectations have been confirmed in the DDI studies.

The following is a consideration of issues related to the efficacy of mirabegron 25 mg versus mirabegron 50 mg:

In Study 178-CL-074, for both co-primary endpoints, mirabegron 25 mg and 50 mg groups (with adjustments for multiplicity) were statistically superior to placebo. Mirabegron 50 mg had a statistically greater increase from baseline to final visit compared to placebo in the mean voided volume while mirabegron 25 mg did not. As a result, subsequent endpoints for mirabegron 50 mg were evaluated at the 0.025 significance level and subsequent endpoints for mirabegron 25 mg were excluded. Mirabegron 50 mg group had a statistically significant greater reduction from baseline to first measured time postdose at week 4 compared to placebo in the mean number of incontinence episodes per 24 hours. Due to the gatekeeping procedure, statistical significance was not achieved or any other secondary safety variables for either treatment group. The gatekeeping procedure notwithstanding, the 4 week efficacy for mirabegron 25 mg with respect to incontinence episodes and micturitions per 24 hours at weeks was not statistically significantly different from placebo, although statistically significant and clinically relevant differences from baseline and from placebo were observed for mirabegron 25 mg at Week 8 and at Week 12.

Based on the above efficacy results, the review team undertook a consideration of 25 mg versus 50 mg of mirabegron as the to-be-administered dose, or a dose regimen of 25 mg starting dose with potential to increase to the 50 mg dose. This involved consideration of the results of the additional secondary endpoints to better inform the primary efficacy data. They are each considered below:

- Overall mirabegron 50 mg achieved more statistically significant endpoints than mirabegron 25 mg.
- Therapeutic effect at 8 weeks, but not at 4 weeks, was demonstrated for mirabegron 25 mg.
- Measures of urgency which include mean level of urgency, mean number of Grade 3 or 4 urgency episodes and change in baseline of mean level of urgency all showed a numerical reduction for mirabegron 50 mg, and mean level of urgency was also statistically significantly reduced at endpoint as compared to placebo. With respect to mean level of urgency and mean number of Grade 3 or 4 urgency episodes, while both mirabegron 25

and 50 mg numerically improved these measures, the improvement with mirabegron 50 mg was numerically greater than the 25 mg dose.

- An urgency responder was defined as a patient with a decrease from baseline to final visit in mean level of urgency which was at least as large as the Sponsor's determination of minimally important difference (0.24). At the final visit, the percentage of responders defined this way was greater in the mirabegron 25 mg and 50 mg groups than in placebo. The difference versus placebo was 3.9% for the mirabegron 25 mg group and 8.3% for the mirabegron 50 mg group. The corresponding odds ratio for the mirabegron 25 and 50 mg groups was 1.17 and 1.37, respectively; statistical significance was achieved for the mirabegron 50 mg group.
- In incontinent patients who required pad use, there was a reduction in the mean number of pads used per 24 hours from baseline to final visit; the adjusted mean difference from placebo for the mirabegron 25 mg and 50 mg groups at final visit was 0.16 (more pad use) and -0.17 (less pad use), respectively.
- OAB-q Bother Score: (A negative change in the Symptom Bother score indicated improvement) At the final visit, the adjusted mean difference versus placebo was -1.8 and -2.8 for the mirabegron 25 mg and 50 mg groups, respectively. The reduction from baseline to final visit in the Symptom Bother score was statistically significantly greater in the mirabegron 50 mg group compared to placebo.
- Clinical and Patient Global questions suggest some degree of superiority for the mirabegron 50 mg over mirabegron 25 mg.
- On the WPAI:SHP (Work Productivity and Activity Impairment), a negative change from baseline indicates improvement. Four parameters were assessed: work time missed, impairment while working, overall work impairment and activity impairment. The negative mean change from baseline to week 12 and final visit was greater in the mirabegron 50 mg group compared to placebo for all parameters except overall work impairment.
- Secondary endpoints where no demonstrable differences were noted between mirabegron 25 mg and 50 mg and/or placebo were: nocturia, treatment satisfaction VAS score (both 25 and 50 mg had significant improvement), the Health Related Quality of Life (HRQL), and the EQ-5D.

Reviewer's Comment: Taken all information together, the results for mirabegron 25 mg and 50 mg appear similar at 8 weeks for the primary efficacy endpoints. However, it would appear that mirabegron 50 mg may offer an overall better clinical benefit. therefore, in order to optimize the risk/benefit ratio, a starting dose of 25 mg for all patients, with an 8 week trial, followed by an increase to mirabegron 50 mg in patient with suboptimal improvement in symptoms seems reasonable The 25 mg dose should also be utilized in patients with moderate hepatic or severe renal impairment.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study 178-CL-049 (see individual study review) was a randomized, active controlled, double-blind, double-dummy, long term study that provided evidence to demonstrate the persistence of efficacy for mirabegron. This evaluation included the objective OAB endpoints, patient reported outcomes and responder analyses for both micturitions and incontinence episodes. The inclusion/exclusion/criteria were the same as for the pivotal studies. The analyses of the efficacy endpoints adjusted for prior treatment and study experience. Overall, 74.2% and 85.3% of patients were female (FAS and FAS-I, respectively). The higher proportion of female patients was the major difference in demographics and baseline characteristics observed between the FAS and the FAS-I populations. History and baseline characteristics of OAB were comparable across all treatment groups in the FAS and FAS-I populations.

Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturitions per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours in subjects with baseline incontinence (adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables. Numerically similar results and a similar course of improvement over time were observed with tolterodine ER 4 mg. The reader is referred to Tables 35 and 36 within the review of Study 178-CL-049.

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

Reviewer's Comment: In this safety study, the efficacy of mirabegron 50 and 100 mg once daily doses is maintained and there appears to be no indication of tachyphylaxis.

6.1.10 Additional Efficacy Issues/Analyses

In the primary phase 3 studies, patients were instructed to take medication in the morning with a glass of water, with or without food. Mirabegron 50 and 100 mg were effective when administered without regard to food. The available data in the Mirabegron and Food Effect Report indicate that the effect of food status is of limited clinical relevance and food-specific

additional dosing instructions are not supported, as there was extensive overlap in plasma concentrations between those who took drug between 30 minutes before and 30 minutes after food and those who did not.

Both mirabegron 50 and 100 mg doses were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours in OAB anti-muscarinic treatment naïve patients as well as in patients that had received previous OAB anti-muscarinic therapy. In patients with previous OAB anti-muscarinic therapy, both mirabegron 50 and 100 mg doses were effective in reducing the placebo-corrected mean number of micturitions per 24 hours in patients discontinuing secondary to poor tolerability. In patients with previous OAB anti-muscarinic therapy both mirabegron 50 and 100 mg doses were effective in reducing the placebo-corrected mean number of incontinence episodes and 24 hours in patients discontinuing secondary to poor tolerability. The results were comparable in both instances to the results in the general patient population.

7 Review of Safety

Safety Summary

The studies performed by the Sponsor for the treatment of overactive bladder (OAB) are adequate to assess the safety of mirabegron used once a day for the treatment of OAB. The results largely demonstrate that mirabegron is generally well-tolerated in the treatment of OAB. The data below include information from the August 6, 2011 NDA submission and amendments. In the pivotal and additional analysis sets supporting the OAB indication, the following was the extent of exposure and demographics:

- *Within the 12 Week Phase 2/3 Population which used the OCAS formulation (to be marketed) among the total 4414 subjects, there were 2142 placebo subjects, 811 mirabegron 25 mg subjects, 2131 mirabegron 50 mg subjects, 1305 mirabegron 100 mg subjects and 167 mirabegron 200 mg subjects. There were also 958 subjects who received tolterodine ER 4 mg in active comparator arms.*
- *Other phase 2 studies were of either short duration (2-4 weeks) or were for special purpose (BPH-12 weeks). Within these studies there were 170 placebo subjects, 70 mirabegron 50 mg subjects, 65 mirabegron 100 mg subjects, 145 mirabegron 200 mg subjects, and 65 300 mg subjects.*
- *In the long-term controlled population study (Study 049), 812 patients were exposed to mirabegron 50 mg, 820 patients were exposed to mirabegron 100 mg (of the total 1632, 901 patients were re-exposures) and 812 patients received tolterodine ER 4 mg active comparator.*
- *In the Japanese long-term uncontrolled population 153 patients received mirabegron 50 mg and 50 patients received mirabegron 100 mg as highest dose in this titrated study.*

- *In the global phase 2/3 population, in patients with continuous mirabegron exposure (n=5863), 4191 received mirabegron for ≥ 84 days, 1572 received mirabegron for ≥ 182 days and 622 patients received mirabegron for ≥ 365 days.*
- *In the global phase 2/3 population, 2458 patients received mirabegron for a duration of between 84 and 181 days, 875 patients received mirabegron for a duration of 274-364 days and 603 subjects received mirabegron for ≥ 365 days.*
- *Patients in the primary phase 3 studies (safety analysis set [SAF]) were predominantly female (approximately 72%) and White (approximately 94%) with a mean age of 59 years (range 18-95 years). Approximately 38% of patients were ≥ 65 years of age and approximately 12% of patients were ≥ 75 years of age across the treatment groups.*

There were 11 deaths in the mirabegron program, including 2 deaths in ongoing Study 178-CL-090 (one sudden death on blinded treatment and one death that occurred prior to randomization, chemical poisoning). Nine deaths occurred in patients participating in completed trials (5 patients treated with mirabegron, one treated with placebo and 3 treated with tolterodine). Of the five deaths occurring in patients treated with mirabegron: one patient died due to metastatic colon cancer, one due to pneumonia that progressed to sepsis, respiratory failure, multi-organ failure and renal vein thrombosis, one due to cardiac failure, one due to suicide and one due to aortic dissection. All of these deaths had confounding conditions making attribution to mirabegron problematic. There were three deaths in studies other than the pivotal studies. Brief narratives for each death are included in the Summary of Clinical Safety. Detailed narratives for those patients in a mirabegron treatment arm are provided in the respective individual study reviews in this NDA review. Overall, these deaths are unlikely to be related to mirabegron.

In the OAB 12-week Phase 3 Population, one or more SAEs were reported for 62/2736 (2.3%) mirabegron, 29/1380 (2.1%) placebo and 11/495 (2.2%) tolterodine patients, with no apparent mirabegron dose response. The overall incidence of SAEs in the EU/NA Phase 3 Study population in mirabegron subjects was 23/786 (2.9%) for males and 39/1950 (2.0%) for females. The most common SAEs in the total mirabegron group were atrial fibrillation (mirabegron: 5/2736 [0.2%]; placebo: 1/1380 [0.1%]; tolterodine: 0/495), and chest pain (mirabegron: 4/2736 [0.1%]; placebo: 2/1380 [0.1%]; tolterodine: 0/495.) SAEs occurring in 0.1% of mirabegron 50 mg patients and not in placebo patients and judged to be potentially relevant to mirabegron safety were: angina, pneumonia, humerus fracture, limb injury, radius fracture, malignant melanoma, metastases to lymph nodes, prostate cancer and hypertensive crisis. The malignancies in this reviewer's judgement were pre-existing. The hypertensive crisis was improperly classified. There was one case of angina. The fractures and potential for falls and injury were evaluated and no increased risk was identified with mirabegron when overall case numbers were considered. All but one case of atrial fibrillation in mirabegron patients had confounding conditions.

The most common TEAEs (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%]). 0.1 % of mirabegron patients discontinued secondary to atrial fibrillation or palpitations as did similar percentage in the placebo group. 4 (0.1%) mirabegron patients discontinued due to tachycardia versus none in the placebo group. Abnormal liver function tests resulted in discontinuation in 3 (0.1%) mirabegron patients versus 1 (0.1%) placebo patient. Skin rash was reported in 2 (0.1%) of mirabegron patients leading to discontinuation versus 0 for placebo. A modest increase in overall TEAEs was noted in females as compared to males (female total mirabegron 916/1950 [47.0%] versus 343/786 [43.6%].

In the 12-Week OAB Phase 3 population, TEAEs reported by $\geq 3.0\%$ of patients were hypertension 200/2736 (7.3) of mirabegron patients versus 105/1380 (7.6%) placebo patients, nasopharyngitis 94/2739 (3.4%) versus 35/1380 (2.5%) and UTI 83/2736 (3.0%) versus 25/1380 (1.8%) for placebo. The mirabegron hypertension cases were reviewed and the majority of patients had hypertensive blood pressures noted prior to exposure to mirabegron. In several mirabegron cases, the absolute increase from baseline in BP was notable.

The EU/NA Long-term Controlled Population (consisting of the 1-year Study 049) included 1632 patients treated with mirabegron and 812 patients treated with tolterodine. One or more SAE, TEAE and TEAE leading to permanent discontinuation of study drug were reported by 93/1632 (5.7%), 988/1632 (60.5%) and 98/1632 (6.0%) of mirabegron patients, and 44/812 (5.4%), 508/812 (62.6%) and 46/812 (5.7%) of tolterodine patients, respectively

The following are brief summaries of special safety issues for this application:

Cardiovascular Safety: Mirabegron is a beta adrenergic agonist and as such is expected to increase heart rate. Mirabegron was also associated with a modest increase in blood pressure, which was more notable in Phase 1 studies than in Phase 3 studies. Therefore, the incidence of major adverse cardiovascular events (MACE) was of interest. There were few APTC/MACE events in the entire application (N= 2/4414 for mirabegron, 4/2142 for placebo and 1/958 for tolterodine in the Global OAB Phase 2/3 Population). Although the number of MACE events was small, the relative risk (RR) for the occurrence of APTC/MACE in the Global OAB Phase 2/3 Population shows no evidence of a detrimental effect of mirabegron. The RR was 0.24 (95%CI: 0.02, 1.69) for patients receiving mirabegron compared with placebo. The incidence of TEAEs and SAEs related to hypertension were similar for mirabegron, placebo and tolterodine in the long term study. The absence of a clinically meaningful prolongation of QTc at mirabegron 50 and 100 mg doses was demonstrated both in the pivotal studies and in a dedicated large thorough QT study in healthy male and female volunteers. . Based on the very small incidences, and very small differences between groups, as well as alternative explanations in almost all individual cases, it is unlikely that mirabegron is causative in atrial fibrillation. Study 178-CL-053 did not document a negative inotropic effect of beta-3 agonism which argues against a mirabegron association with cardiac failure. Despite the alternative explanations for tachycardia and palpitations in several patients, and lack of vital sign data in several cases, we conclude that these AEs are plausibly related to mirabegron.

In the Phase 3 studies, mirabegron at the proposed therapeutic dose of 50 mg once daily was associated with an approximately 1 bpm increase in adjusted mean change from baseline pulse compared to placebo. Categorical increases from baseline in SBP and DBP for the EU/NA OAB 12-Week Phase 3 and the EU/NA Long-term Controlled Study 178-CL-049 populations were generally comparable across all treatment groups. However, in one of the three Phase 3, placebo-controlled studies, small categorical increases from baseline in blood pressure (≥ 5 and ≥ 10 mmHg). Also in Phase 3 studies, there was a modest average increase from baseline in pulse rate (approximately 1-2 bpm) with mirabegron over placebo. Categorical increases from baseline (≥ 2 , ≥ 5 , ≥ 10 or ≥ 15 bpm) in pulse rate in the 12 week pivotal studies were noted more frequently at various cut points with mirabegron than with placebo.

In order to gain some idea of the impact of these very small blood pressure effects on serious cardiovascular outcomes, individual patient blood pressures were placed into the Framingham Risk Model analysis. The small increase in blood pressure associated with mirabegron was predicted to result in a very small increase in the number of serious cardiovascular events over an extended period of time. The risk was believed to be most relevant in patients with markedly high blood pressure at baseline. It would be reasonable to craft appropriate cautionary labeling and to investigate this issue further in a postmarketing cardiovascular outcomes epidemiology study.

CNS Safety: In the Phase 3 and Long-term studies no event of seizure occurred in a mirabegron subject. In the Phase 3 studies syncope was noted in 2/435 (0.5%) of mirabegron 25 mg subjects and 2/1375 (0.2%) of mirabegron 50 mg subjects versus 1/1380 (0.1%) of placebo subjects. Postural hypotension was noted in one mirabegron 25 mg subject and no other treatment arm. Fall were noted in 13/432 (3.0%) mirabegron 25 mg subjects, 31/1375 mirabegron 50 mg subjects and 23/1380 (1.7%) of placebo subjects. There was no evidence of CNS changes playing a roles in these falls.

Neoplasms: In the pivotal studies, there was a small difference between mirabegron and placebo in total number of neoplasm AEs when a variety of tumors, most reported by just one patient each, were added together. In the EU/Long-Term Study (Study 049), a higher incidence of SAEs reported as “neoplasms” was also observed in the mirabegron 100 mg group (1.3%) compared to the mirabegron 50 mg group (0.1%) and the tolterodine group (0.5%) in the EU/NA Long-term Study. Upon review and after oncologic consultation, it appears likely that most, and perhaps all of the neoplasms noted in Study 178-CL-049 were preexisting, based on the known mechanisms of carcinogenesis and known length of time that tumors take to grow to a sufficient size to cause symptoms or permit detection. Nonetheless, there is a discrepancy between the incidence in the 100 mg group and either the 50 mg or tolterodine groups. It should be noted that the increased incidence of neoplasms, while of some concern, did occur in the 100 mg mirabegron dose group and not in the to be marketed 50 mg dose group, and the starting 25 mg dose will be even lower. It would be reasonable to investigate this unlikely but potential safety issue further through a postmarketing epidemiology study.

Urinary Tract Safety: *The data demonstrate that mirabegron is not associated with urinary retention (AUR) or increases in PVR volume. 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 Qmax or PdetQmax. While this does not provide sufficient evidence to support a claim of safety in men with bladder outlet obstruction, it is somewhat reassuring. The frequency of UTI was higher in mirabegron patients compared with placebo patients in the 12-week studies and similar to tolterodine patients. There was no evidence of a mirabegron dose response. Three urolithiasis SAEs (renal colic) were reported in the mirabegron group versus none in placebo in the EU/NA 12-Week, Phase 3 Population, although it is likely that stones were present in these three patients prior to initiation of mirabegron.*

Hepatic Safety: *In the 12-Week Phase 3 Population, one mirabegron 25 mg, one mirabegron 50 mg patient and one tolterodine patient had hepatic adverse events reported. Of the mirabegron patients, one had hepatitis A, B, and C (this patient also participated in the Long-term study). The other mirabegron patient was taking concomitant drugs that have been associated with hepatotoxicity. Three mirabegron patients in the Long-term study had hepatic adverse events reported. One of these patients was the patient with hepatitis A, B, C from the pivotal Phase 3 studies. During the Long-term study, his liver enzyme elevations met Hy's Law criteria. One of the other hepatic AE patients in the Long-term Study underwent liver biopsy secondary to enzyme elevations not meeting Hy's Law. The biopsy result was compatible with either auto-immune hepatitis or drug induced hepatic injury. This patient was taking an herbal medication that may have played some role in the event. The last hepatic AE patient in the long term study had liver enzyme elevations in association with a hypersensitivity reaction of hemolytic anemia. In a non-phase 3 study, a female patient had liver enzyme elevations in association with Stevens Johnson Syndrome while taking mirabegron. This patient met Hy's Law criteria. Overall, then, there may have been two cases of hepatotoxicity in patients who taking mirabegron, who also sustained a hypersensitivity reaction.*

In addition, two patients in the Long-term Study had rises of the ALT and AST to 10 times ULN with return to normal or to baseline levels while continuing to take mirabegron 50 mg.

Currently, the evidence is not sufficient to state that mirabegron is associated with hepatotoxicity; however, a very small number of severe hepatic adverse events were reported during clinical trials.

Hypersensitivity Reactions: *The incidence of plausibly related hypersensitivity reaction events was higher in mirabegron subjects than it was in placebo subjects. There was one non-serious case of immediate hypersensitivity in a 100 mg mirabegron patient (pruritis). There were no cases of anaphylaxis or angioedema. In the non-immediate hypersensitivity category, there were 7 reports in mirabegron 50 mg subjects, 3 in mirabegron 25 mg subjects, one in a placebo subject, and three in tolterodine subjects. In two patients (one taking mirabegron 100 mg and one taking mirabegron 50 mg), leukocytoclastic vasculitis was reported. In terms of non-immediate primarily noncutaneous hypersensitivity reactions, one patient (mirabegron*

100 mg) sustained hemolytic anemia and thrombocytopenia. There were also two 100 mg subjects who had an undetermined type of hypersensitivity reaction. An additional patient, 178-CL-049, 1630-6655 exposed to mirabegron 100 mg had liver biopsy changes compatible with drug induced hepatic injury or autoimmune hepatitis. This patient, who had been taking a concomitant herbal supplement with previous reports of hepatic adverse reactions, has been described previously. In the postmarketing period in Japan, there have been two reports of erythema multiforme in patients taking mirabegron, but there are no available details for these 2 cases. Taken together, it appears that delayed hypersensitivity reactions are a potential risk of mirabegron. This is evidenced by 2 cases of erythema multiforme (post marketing listing from Japan), 1 case of Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, 1 case of hemolytic anemia and 1 case of possible autoimmune hepatitis where an herbal supplement may have played a role.

Glaucoma/Increased Intraocular Pressure: Despite adverse event reports of “increased intraocular pressure” and “glaucoma”, mirabegron did not increase intraocular pressure more than placebo, as shown in a dedicated study involving 310 healthy volunteers.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety analysis will concentrate on the safety results in the EU/NA 12-week Phase 3 population (Studies 178-CL-046, 178-CL-047, and 178-CL-074) and the controlled population of longest duration, the EU/NA Long-term Controlled Population (Study 178-CL-049). Certain other phase 2 or phase 3 studies may be referred to as needed in integrated form or individually (these 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-049, 178-CL-051, and 178-CL-060). The reader is referred to Table 2 of this review for summaries of each study.

The Sponsor states the total number of unique mirabegron patients in the Global Phase 2/3 Population is $4414+345+901+203=5865$. This population includes all patients who received at least one dose of mirabegron in a phase 2/3 study. The 12 studies included in this population were of varying durations (4 weeks, 12 weeks, 52 weeks [12 months]), varying indications (OAB, LUTS/BOO, type 2 diabetes mellitus), varying mirabegron formulations (IR, OCAS), and varying study designs (mostly double-blind, but some open-label) and varying geographic locations (Europe, North America, Japan, Australia/New Zealand, South Africa).

*Reviewer’s Comment: There is also a categorization of studies listed as the **Global Phase 2/3 12 week OAB** population. Where possible, the primary focus of safety analysis will be the EU/NA 12-week Phase 3 population. Occasionally the Global Phase 2/3 12 week OAB population will be referred to as it is a larger numerical group and may better inform the safety discussion.*

The Sponsor has also provided detailed summaries for AEs of special interest – for example, cardiovascular (CV) system, hypersensitivity reactions, glaucoma/increased intraocular pressure and neoplasm. These research reports were reviewed and will be considered in this integrated review of safety.

Table 63: Patients Treated in the Phase 2/3 Clinical Population

Study	Treatments								
OAB 12-Week Phase 2/3 Population									
		Total Daily Dose of Mirabegron							
	Placebo	25mg	50mg	100mg	200mg	Total Mirabegron	Tolterodine ER 4mg		
178-CL-046	494		493	496		989	495		
178-CL-047	453		442	433		875			
178-CL-074	433	432	440			872			
Phase 3 Total 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 in the Phase 2/3 Population									
		Placebo	25mg	50mg	100mg	200mg	300mg	Total	Tolterodine ER 4mg
178-CL-003	19					40		40	
178-CL-004	20					40		40	
178-CL-008	66					65	65	130	64
178-CL-060	65		70	65				135	
Totals	170		70	65	145	65	65	345	64

Source: Table 4, Summary of Clinical Safety, current submission, page 23

Table 64: Long Term Controlled Population

Study	Mirabegron mg/day		New Exposure	Re-Exposure	Tolterodine ER 4 mg
	50mg	100mg			
178-CL-049	812	820	901	731	812
Total Mirabegron Exposure =1632					
Japan Long-Term Uncontrolled Population					
178-CL-051	50 mg (only)	100 mg (used)			
	153	50			
Total Mirabegron Exposure=203					

Source: Table 4, Summary of Clinical Safety, current submission, page 23

7.1.2 Categorization of Adverse Events

The adverse events were analyzed in the following categories:

- Deaths
- Other serious adverse events
- Discontinuations due to adverse events
- Commonly reported adverse events
- Adverse events in the following situations
 - Ethnicity
 - Diabetes (as an intrinsic factor)
 - Renal Impairment (as an intrinsic factor)
 - Hepatic Impairment
 - Gender
 - Subgroups based on age (as an intrinsic factor)
 - Race
 - Body Weight
 - Benign Prostatic Hypertrophy
 - Geographical Region
 - Fed Fasting Food Status-Sponsor submitted research report
- Other adverse events of interest, which include:
 - Cardiovascular events-Sponsor submitted research report
 - Eye Disorders-Sponsor submitted research report
 - Urinary Tract Events (UTI, Retention, Urolithiasis)
 - Increases in Transaminases/Hepatotoxicity
 - Hypersensitivity-Sponsor submitted research report
 - Endocrine and metabolic disorders
 - Neoplasms-Sponsor submitted research report
- Extrinsic Factors
 - Concomitant Antihypertensive Drug Use
 - CYP3A4 Inhibitor Use
 - Current Use of Alpha-Blocker Therapy
- Vital Signs

Reviewer's Comment: Overall categorization of events appeared to be consistent, and there did not appear to be lumping or splitting.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were analyzed separately for each study listed in these sNDA submissions (see individual study reviews) and data was pooled for the integrated analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 65 summarizes the patient exposure to mirabegron.

Table 65: Summary of Mirabegron Exposure: Global Phase 2/3 Population

Characteristic n(%) of Patients		Continuous Exposure of Total Mirabegron (n=5863)
Duration of Exposure (days)	≥7	5800
	≥14	5740
	≥28	5625
	≥56	5296
	≥84	4191
	≥182	1572
	≥274	1482
	≥365	622
Duration Category (days)	1-6	53
	7-13	60
	14-27	115
	28-55	329
	56-83	1105
	84-181	2619
	182-273	90
	274-364	860
	≥365	622
Duration (days)	Mean(SD)	152.0 (125.78)
	Median	85.0
	Min, Max	1, 396
Patient –years of exposure	Total	2439.44

Source: Table 10, Integrated Summary of Safety, Page 61

Reviewer’s Comment: The overall patient exposure to mirabegron and duration of exposure far exceeds ICH Guidance criteria for a new molecular entity, and is adequate to estimate safety of mirabegron at the to be marketed doses.

In the Global Phase 2/3 Population, 4399/5863 (75.0%) mirabegron patients were female. Overall, 4387/5858 (74.9%) patients were White, 1259/5858 (21.5%) were Asian,

179/5858 (3.1%) were Black or African American and 33/5858 (0.6%) were “Other”; 2655/2783 (95.4%) were not Hispanic or Latino. The percentage of Asian patients varied widely among dosage groups, ranging from 0% to 28.5% among mirabegron treatment groups, 28.3% for placebo and 39.9% for tolterodine.

The median age was 60.0 years of age; 2095/5863 (35.7%) patients were ≥ 65 years of age and 574/5863 (9.8%) patients were ≥ 75 years of age. The mean height was 164.4 cm, the mean weight was 74.78 kg and the mean body mass index (BMI) was 27.5 kg/m². The largest proportion of patients were in the < 25 kg/m² BMI group (2231/5862 [38.1%]) and were from Europe (2831/5863 [48.3%]).

Within the European/North American (EU/NA) 12 week Phase 3 Population, across all treatment groups, 3313/4611 (71.9%) were female patients. Overall, 4310/4611 (93.5%) patients were White, which is higher than that of the Global OAB 12-week Phase 2/3 Population (5220/7508 [69.5%]). Overall, 223/4611 (4.8%) patients were Black or African American, 49/4611 (1.1%) were Asian and 29/4611 (0.6%) were “Other”; 2484/2633 (94.3%) of patients were not Hispanic or Latino. The median age was 61.0 years of age; 1744/4611 (37.8%) patients were ≥ 65 years of age and 499/4611 (10.8%) patients were ≥ 75 years of age. The mean height was 166.4 cm, the mean weight was 80.33 kg and the mean BMI was 29.0 kg/m². The largest proportion of patients were in the 25 to < 30 kg/m² BMI group (1715/4608 [37.2%]) and were from Europe (2565/4611 [55.6%]); all tolterodine patients (495/495 [100%]) were from Europe.

In the EU/NA Long-term Controlled Population (Study 049), the demographic and baseline characteristics (recorded at baseline for Study 178-CL-049) were consistent across treatment groups. Overall, 1810/2444 (74.1%) patients were female, 2332/2444 (95.4%) patients were White and 2367/2442 (96.9%) patients were non-Hispanic and non-Latino. The median age was 61.0 years of age. Overall, 908/2444 (37.2%) patients were ≥ 65 years of age and 239/2444 (9.8%) patients were ≥ 75 years of age. The mean height was 166.3 cm, the mean weight was 79.59 kg and the mean BMI across all treatment groups was 28.8 kg/m². The largest proportion of patients were in the 25 to < 30 kg/m² BMI group (941/2439 [38.6%]) and were from Eastern Europe (788/2444 [32.2%]).

Intrinsic and extrinsic factors were comparable across all treatment groups in the Global OAB 12-week Phase 2/3 Population (consisting of 6 trials: Phase 3 Studies 046, 047 and 074 plus the Phase 2B multinational Studies 044, and the Japanese Phase 2 and Phase 3 Studies 044 and 048, respectively) for the 25, 50, and 100 dose groups of mirabegron.

Reviewer’s Comment: The Phase 3 study population was similar to those of other approved OAB products and consisted predominantly of older, White women.

7.2.2 Explorations for Dose Response

The EU/NA OAB 12-week Phase 3 Population includes 2736 patients treated with mirabegron, 1380 patients treated with placebo and 495 patients treated with tolterodine. One or more SAE,

TEAE and TEAE leading to permanent discontinuation of study drug were reported by 62/2736 (2.3%), 1259/2736 (46.0%) and 104/2736 (3.8%) mirabegron, 29/1380 (2.1%), 658/1380 (47.7%) and 46/1380 (3.3%) placebo, and 11/495 (2.2%), 231/495 (46.7%) and 22/495 (4.4%) tolterodine patients, respectively. There was no apparent dose response across mirabegron groups. These trends were similar to those observed with the Global OAB 12-week Phase 2/3 Population.

Table 66: Adjusted Mean Difference versus Placebo for Primary Endpoints (Pooled Pivotal Studies) from Baseline to Final Visit

Co-Primary Efficacy Results	Placebo n=1380	Mirabegron			
		25 mg n=254	50 mg n=862	100 mg n=577	200 mg n=167
Adjusted Mean Difference Vs placebo from Baseline to Final Visit		Incontinence Episodes per 24 hours			
		-0.40	-0.40	-0.41	-0.58
	p value	# 0.005	# <0.001	# <0.001	0.0551
		Mean Number of Micturition per 24 hours			
		-0.47	-0.55	-0.54	-0.80
	p value	# 0.007	# <0.001	# <0.001	0.0041

= corrected for multiplicity. The placebo number is from phase 3 pooled data. The efficacy data for mirabegron 200 mg is from study 178-CL-044.

Sources: Table 1, Clinical Overview, Page 34

Table 67: Adverse Events Based upon Dose EU/NA Phase 3 Pivotal Studies (Pooled Data)

n (%) Patients	Placebo (n=1380)	Mirabegron				Tolterodine ER 4 mg (n=495)
		25 mg (n=432)	50 mg (n=929)	100 mg (n=929)	Total (n=2736)	
Deaths	1 (0.1)	0	0	1 (0.1)	1 (<0.1%)	1 (0.2%)
SAE	29 (2.1)	7 (1.6)	29 (2.1)	26 (2.8)	62 (2.3)	11 (2.2)
TEAE leading to Discontinuation	46 (3.3)	17 (3.9)	53 (3.9)	34 (3.7)	104 (3.8)	22 (4.4)
TEAE	658 (47.7%)	210 (48.6%)	647 (47.1%)	402 (43.3%)	1259 (46.0%)	231 (46.7%)

Source: Table 30, ISS, page 99, ISS Table, 5.1.3 and Study Report 178-CL-046

In the Global OAB 12-Week Phase 2 and 3 Population, 167 patients received mirabegron 200 mg a day (Study 178-CL-044). There were no deaths in this group. There were 3 SAE's (1.8%). 7 patients (4.2%) discontinued secondary to an AE. 80 (47.9%) patients experienced an adverse event while using mirabegron 200 mg (Table 5.1.2 ADAE dataset, ISS/SCS).

Reviewer's Comment: The Sponsor has conducted adequate dose exploration for dose response for safety and efficacy. Based on risk and benefit, the reviewer agrees with the selected to-be-marketed doses of 25 mg and 50 mg.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate based on the drug's pharmacology and clinical findings that emerged in clinical development.

7.2.4 Routine Clinical Testing

The safety assessments included: AEs, clinical laboratory measurements (hematology, urinalysis, chemistry and PSA), vital signs (sitting vital signs, including diastolic blood pressure [DBP], systolic blood pressure [SBP], and heart rate), post-void residual urine volume and urodynamics, physical examination including digital rectal examination (DRE). These were recorded at each study visit in the double-blind periods of each study and periodically throughout the active-controlled safety Study 049.

7.2.5 Metabolic, Clearance, and Interaction Workup

A number of drug drug interaction (DDI) studies were conducted with mirabegron and the reader is referred to the Clinical Pharmacologist's review for details of these studies. Some clinically relevant findings from these studies are provided here.

Based on in vitro studies, mirabegron was predicted to inhibit CYP2D6; therefore DDI studies were conducted with the CYP2D6 substrates metoprolol and desipramine (Study 178-CL-005 and 178-CL-058). The impact of CYP2D6 on metabolism of mirabegron was also assessed by studying pharmacokinetics in poor and extensive metabolizers of CYP2D6 in Study 005. The observed increase in C_{max} and AUC of YM178 in the poor metabolizers compared to the extensive metabolizers was minimal and was deemed not clinically relevant. However, administration of 160 mg mirabegron for 5 days resulted in a statistically and clinically significant increase in C_{max} and AUC_{0-inf} of metoprolol after a single dose of 100 mg metoprolol compared to these values in absence of YM178. The data suggest that mirabegron reduces the clearance of metoprolol by inhibition of CYP2D6 and increases its bioavailability by a reduced first-pass effect.

In Study 1787-CL-006, metformin (500 mg b.i.d.) minimally decreased C_{max} and AUC_{0-24h} steady state values of mirabegron (160 mg q.d). Mean t_{max} and CLR were not affected. The presence of mirabegron did not result in a change in the pharmacokinetics of metformin, except for a small decrease of C_{max} that was not considered to be of clinical importance. The Sponsor concludes that the data indicate that combining metformin and mirabegron does not result in a clinically relevant pharmacodynamic interaction on fasting plasma glucose (FPG) or HbA_{1c} levels, or on any of the secondary pharmacodynamic parameters.

In Study 178-CL-058, the effect of multiple doses of mirabegron on the pharmacokinetics of desipramine was evaluated. Administration of mirabegron 100 mg q.d. for 19 days resulted in a 3.41-fold (90% CI: 3.07 to 3.80) increase in the AUC_{inf} and a 1.79-fold (90% CI: 1.69 to 1.90) increase in the C_{max} of a single dose of 50 mg desipramine. 15 days after YM178 discontinuation, the mean ratios and 90% CIs of AUC_{inf} and C_{max} for desipramine fell within the pre defined boundaries of 0.80 to 1.25; mean values of the other pharmacokinetic parameters returned to baseline for desipramine and 2 hydroxydesipramine.

Reviewer's Comment: The findings for desipramine and metoprolol should be described in labeling.

The effects of multiple doses of YM178 on the PK of ethinyl estradiol (EE) and levonorgestrel (LNG) containing oral contraceptives was evaluated in Study 178-CL-068. In the presence of mirabegron, slightly lower steady state EE and LNG plasma concentrations were observed relative to the oral contraceptive given alone. The ratio of least square means for C_{max} and AUC_{tau} values (with and without mirabegron) were 0.958 and 0.961 for EE, and 0.938 and 0.955 for LNG. The boundaries for the 90% confidence intervals were contained entirely within the predefined limits (0.80 to 1.25) for equivalence, indicating that there is no relevant effect of mirabegron on the levels of EE or LNG. The Sponsor concludes that co-administration of mirabegron 100 mg qd and COC did not affect the steady state pharmacokinetics of EE and LNG.

Study 178-CL-059 evaluated the effect of multiple doses of mirabegron on the pharmacokinetics of digoxin in healthy subjects. The C_{max} and AUC_{last} of digoxin (single 0.25 mg dose) were increased by 1.29-fold and 1.27-fold in combination with mirabegron compared to digoxin alone. Because the intervals exceed the pre-specified interval of 0.80 – 1.25, a clinically relevant effect of YM178 on digoxin pharmacokinetics cannot be excluded.

Reviewer's Comment: In light of the narrow therapeutic index of digoxin this result should be described in labeling.

The effect of YM178 on the pharmacokinetics of warfarin was evaluated in Study 178-CL-040. Steady state plasma concentrations of mirabegron (100 mg q.d.) were achieved at Day 23 and maintained after a single dose of 25 mg warfarin. Steady state plasma concentrations of mirabegron (100 mg q.d.) had no effect on the PK of either R- or S-enantiomers of warfarin when the racemate was administered as a single 25-mg dose. The mean ratios for C_{max} were 1.05 and 1.04 (R- and S-warfarin, respectively) and for AUC_{inf} were 1.10 for both R- and S-warfarin; the bounds of the 90% CIs were contained within the predefined limits for equivalence (0.80 – 1.25).

Study 178-CL-069 investigated the effects of steady-state mirabegron on the pharmacokinetics of solifenacin in health male and female subjects. Co-administration of mirabegron 100 mg qd increased the C_{max} and AUC_{inf} of solifenacin by 23% and 26%, respectively, without any relevant effect on t_{max}. The increase in solifenacin exposure was accompanied by an increase in

mean $t_{1/2}$ of approximately 3.5 hours. Mean mirabegron C_{max} was not impacted by concomitant solifenacin. Systolic blood pressure increases following co-administration of mirabegron and solifenacin (4.3 and 4.0 mmHg) were similar to those observed with mirabegron alone (3.6 mmHg). Diastolic blood pressure decreases following mirabegron alone (-3.1 mmHg) were similar to co-administration of mirabegron during repeated solifenacin administration (-1.9 mmHg). Heart rate increases following co-administration of mirabegron and solifenacin (8.8 and 10 bpm) were similar to those observed with mirabegron alone (6.6 bpm).

The cardiovascular interaction between mirabegron and tamsulosin were evaluated in Study 178-CL-080. The Sponsor concluded, "In each treatment arm, there was no change in SBP and a small decrease in DBP in the combination dosing group compared to each drug alone. Taken together, the CV results do not suggest a clinically relevant pharmacodynamic interaction between tamsulosin and mirabegron. This is further supported by balanced AE and orthostatic events across all treatment groups. In addition, combination treatment of mirabegron and tamsulosin did not appear to affect the safety profiles of either of these drugs. The higher exposure to tamsulosin following combination treatment of mirabegron and tamsulosin is not reflected by an overt change in safety profile of tamsulosin. Similarly, the reduction of exposure to mirabegron with combination administration of tamsulosin and mirabegron is not reflected by a change in safety profile in mirabegron."

Study 178-CL-041 evaluated the effect of food on the PK of mirabegron in US subjects. Food decreased peak and systemic exposures to mirabegron from the OCAS tablets, which appeared to be similar for both doses and both sexes. None of the 90% confidence intervals for exposure parameters were contained within the equivalence limits of 80.0% to 125.0%. With 50 mg tablets, the ratio and 90% CI values for AUC_{inf} and C_{max} of mirabegron were 17% lower (90% CI of the GM ratio: 74.16, 93.42) and 45% lower (90% CI of the GM ratio: 43.69, 68.65), respectively, after the high-fat breakfast. The low-fat breakfast reduced the mean AUC_{inf} and C_{max} by 51% and 75%, respectively. Food delayed the mean time to peak mirabegron concentration by 1 to 2 hours compared with fasted conditions. The Phase 3 studies were conducted with dosing without regard for food intake.

The effects of age and gender upon the safety and tolerability were evaluated in Study 178-CL-072. Across the tested dose range, mean C_{max} and AUC_{tau} were 44% and 38% higher in females compared with males. A large percentage of this difference is attributable to body weight and less to gender. There were no age-related differences in mean C_{max} and AUC_{tau} of mirabegron.

Study 178-CL-038 evaluated the PK of mirabegron in patients with renal impairment. The Sponsor found that relative to volunteers with normal renal function, systemic exposures to mirabegron (AUC_{inf}) were increased 31% in volunteers with mild renal impairment, 66% in volunteers with moderate renal impairment and 118% in volunteers with severe renal impairment. Systemic exposures to unbound mirabegron ($AUC_{inf, u}$) were increased by 26%, 38% and 84% in volunteers with mild, moderate and severe renal impairment, respectively, compared with the normal renal function group. Renal impairment affected mirabegron C_{max} , but to a lesser degree than AUC_{inf} . Peak exposures to mirabegron were increased by 6%, 23%

and 92% in the mild, moderate and severe groups, respectively, compared with the normal group. Peak exposures to unbound mirabegron were unchanged in the mild group, but increased 2% and 62% in the moderate and severe groups, respectively, compared with the normal group.

The effects of hepatic impairment on the PK of mirabegron were also investigated. The Sponsor concludes that in subjects with mild hepatic impairment, mean C_{max} and AUC_{inf} values of mirabegron following a single 100 mg dose were increased by approximately 1.09-fold (90% CI: 0.42, 2.80) and 1.19-fold (90% CI: 0.69, 2.05) compared to subjects with normal hepatic function. Moderate hepatic impairment resulted in mean C_{max} and AUC_{inf} values that were 2.75-fold (90% CI: 1.08, 6.98) and 1.65-fold (90% CI: 0.95, 2.85) higher, respectively, compared to subjects with normal hepatic function.

Reviewer's Comment: The Sponsor has performed appropriate and adequate studies to evaluate drug interactions with YM178, its metabolism and its clearance.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no currently approved beta-3-adrenoreceptor agonists approved for the US market. Mirabegron was recently approved in Japan.

7.3 Major Safety Results

7.3.1 Deaths

There were 11 deaths in the mirabegron program, including 2 deaths in ongoing Study 178- CL-090 (one death on blinded treatment and one death that occurred prior to randomization). Nine deaths occurred in patients participating in completed trials (5 patients treated with mirabegron, one treated with placebo and 3 treated with tolterodine). All 9 deaths were adjudicated by the Cardiovascular Adjudication Committee. The eight deaths in the 3 pivotal studies and the 52 week long-term safety study are listed in the table below. The detailed narratives for those patients in a mirabegron treatment arm may be found in the respective individual study reviews in this NDA review.

Of the 11 deaths, three occurred in studies other than the 4 “pivotal” studies.

The Sponsor provided brief narratives for each death and they are presented here:

- Patient No. 178-CL-047, U00016176141, 66-year-old woman treated with mirabegron 100 mg, died due to metastatic colon cancer (day 99, nontreatment-emergent). Death occurred > 30 days after the last dose of study drug.
- Patient No. 178-CL-049, 1530-6120, 64-year-old woman treated with mirabegron 50 mg, the clinical course was consistent with overwhelming methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia that eventually progressed to sepsis, respiratory failure, multiple organ failure, disseminated intravascular coagulopathy and

death (day 108, treatment-emergent). The patient had a long-standing history of scleroderma and was taking plaquenil for rheumatoid arthritis.

- Patient No. 178-CL-049, 3034-2380, 72-year-old woman treated with mirabegron 50 mg, had significant cardiac risk factors that included a long-standing history of diabetes mellitus and hypertension, experienced fatal cardiac failure (day 190, treatment emergent). Autopsy results revealed chronic cardiac insufficiency as evidenced by severe coronary artery stenosis and pulmonary edema.
- Patient No. 178-CL-049, 3063-3438, 27-year-old woman treated with mirabegron 50 mg, had reported significant history of depression, personality disorder (borderline) and nervous breakdown, and completed suicide through overdose with anxiolytics and antidepressants. The patient's suicide appeared to be motivated by recent pregnancy (confirmed on autopsy) and suspicion of disseminated sclerosis (unconfirmed). Death occurred 93 days after the last study drug kit was dispensed at the month 9 visit (day 266, nontreatment-emergent).
- Patient No. 178-CL-051, S01503, 59-year-old woman treated with mirabegron 50 mg/100 mg, the cause of death was aortic dissection, and it was estimated that the patient died within minutes of onset. Although the patient's blood pressure was somewhat high, both before and after initiation of study drug treatment, it fluctuated only slightly over a tolerable range with no sudden elevations. The investigator considered the aortic dissection to be not related to the study drug because no signs or symptoms suggesting that this event would occur were observed before or after study treatment initiation, and there were no remarkable abnormalities or abnormal changes in laboratory test values. However, there was insufficient information at the time of the event because the patient was dead on arrival at the hospital, and the Sponsor concluded that the event (aortic dissection), which occurred during study treatment, was not completely unrelated to the study drug (day 237, treatment-emergent). This death occurred in a 52 week safety protocol in Japan and was the only death in the protocol.
- Patient No. 178-CL-047, U00015976697, 76-year-old woman treated with placebo, died due to cardiac arrest 56 days after the last dose of study drug (day 142, nontreatment-emergent). Death occurred > 30 days after the last dose of study drug.
- Patient No. 178-CL-046, 3105-1598, 74-year-old man treated with tolterodine, died due to a ruptured cerebral aneurysm on day 70 (treatment-emergent), 10 days after the last dose of study drug was administered.
- Patient No. 178-CL-049, 1838-6486, 57-year-old woman treated with tolterodine, had a long-standing (17-year) history of cardiovascular disease and experienced probable fatal coronary artery disease (CAD) (died in her sleep on day 208, treatment-emergent).
- Patient No. 178-CL-049, 2190-6983, 68-year-old man treated with tolterodine, had significant history of CAD, diabetes mellitus and hypercholesterolemia. He experienced a cerebrovascular event, which was complicated by concurrent aspiration pneumonia leading to increasing respiratory distress, and ultimately, multiorgan failure and death (day 72, treatment-emergent). This patient also received mirabegron 100 mg in Study 178-CL- 047.

Deaths in ongoing studies:

Prior to Randomization:

- Patient No. 178-CL-090, 90724 (ongoing study), 55-year-old woman, died due to chemical ingestion toxicity, nonaccidental, prior to randomization during the placebo run-in period.

Treatment Group Blinded

- Patient No. 178-CL-090, 90701 (ongoing study), 57-year-old man, received blinded study drug (either placebo or mirabegron 50 mg once daily) for 43 days and experienced sudden death; myocardial infarction was suspected.

Table 68: Listing of Deaths in Phase 3, 12 Week Population, and 52 Week Safety Study

Study, Patient Number, Gender, Age, Drug Dose	MedDRA (v(12.1) Preferred Term	Onset/Day of Last Dose Mirabegron	Day of Death
Mirabegron			
178-CL-047, U000016176141 Female 66 Mirabegron 100 mg	Bladder Cancer, Colon Cancer metastatic	38/49	99
178-CL-049, 1530-6120 Female 64 Mirabegron 50 mg	Pneumonia, Acute Respiratory Failure, Multi-Organ Failure, Renal Vein Thrombosis, Staphylococcal Sepsis	107/85	108
178-CL-049, 3034-2380, female, 72, Mirabegron 50 mg	Cardiac Failure	190/190	190
178-CL-049, 3063-3438, female, 27, Mirabegron 50 mg	Completed Suicide	359/267	359
Placebo			
178-CL-046, U00015976697, female, 76	Cardiac Arrest	142/86	142
Tolterodine ER 4 mg			
178-CL-046, 3105-1598, Male, 74	Ruptured Cerebral Aneurysm	68/70	70

178-CL-049, 1836-6486, Female, 57, (12 weeks mirabegron 50 mg in prior Study 178-CL-047)	Coronary Artery Disease	208/208	208
178-CL-049, 2190-6983, Male, 68 (12 weeks mirabegron 100 mg in prior Study 178-CL-047)	Cerebrovascular Accident	62/62	72

Source: Table 38, ISS, page 123

Reviewer's Comment: Upon review, the cases of colon cancer and suicide can not be attributed to mirabegron. The remaining two mirabegron deaths (cardiac failure, multi-system organ failure with sepsis) were examined detail. Subject 3034-2380 who died of congestive failure, had risk factors of diabetes and hypertension. Based on the circumstances of her death medical details prior to her death are not available. A causal association between mirabegron and her death, while unlikely, cannot be ruled out. With respect to patient 1530-6120, the patient suffered from paralysis since an unknown date, peripheral vascular disease since an unknown date, scleroderma and rheumatoid arthritis(both since 1993) and Raynaud's disease since September 2007. She was treated with Plaquenil which has been associated with blood dyscrasias. This case is significantly confounded and makes a causal association with mirabegron problematic.

Two of the deaths in the tolterodine arm had previously been on mirabegron; however, it would be difficult to attribute those events to mirabegron.

In ISS Table 39, page 127, it is notable that the mortality incidence by patient groups is lower for mirabegron than for placebo and tolterodine. The review of deaths does not raise any new safety concerns.

7.3.2 Nonfatal Serious Adverse Events

In the Global OAB 12-week Phase 2/3 Population, one or more SAE was reported for 77/4414 (1.7%) mirabegron, 38/2142 (1.8%) placebo and 16/958 (1.7%) tolterodine patients, with no apparent mirabegron dose response.

The most common SAEs in the total mirabegron group were atrial fibrillation (mirabegron: 5/4414 [0.1%]; placebo: 1/2142 [$< 0.1\%$]; tolterodine: 0/958), chest pain (mirabegron: 4/4414 [0.1%]; placebo: 2/2142 [0.1%]; tolterodine: 0/958) and pneumonia (mirabegron: 4/4414 [0.1%]; placebo: 1/2142 [$< 0.1\%$]; tolterodine: 0/958). SAE reports in the EU/NA OAB 12-week Phase 3 Population were consistent with those in the Global OAB 12-week Phase 2/3 Population. The overall incidence of SAEs in the EU/NA Phase 3 Study population in mirabegron subjects was 23/786 (2.9%) for males and 39/1950 (2.0%) for females. The table below highlights the SAEs noted in the 12 week EU/NA Phase 3 pivotal studies:

Table 69: Serious Treatment Emergent Events in Safety Analysis Set (MedDRA v12.1): Selected Preferred Terms where Incidence Exceeds Placebo by Dose: Phase 3 EU/NA 12 Week Study Population

System Organ Class (MedDRA 12.1) Preferred Term n (%)	Placebo N=1380	Mirabegron				Tolterodine ER 4 mg N=495
		25 mg N=432	50 mg N=1375	100 mg N=929	Total N=2736	
Overall	29(2.1%)	7(1.6%)	29(2.1%)	26(2.8%)	62(2.3%)	11(2.2%)
Blood and Lymphatic System	0	0	0	1 (0.1)	1 (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
Supraventricular Tachycardia	0	0	0	1 (0.1)	1 (0.1)	0
Eye Disorders	0	0	1 (0.1)	0	1 (0.1)	0
Retinitis	0	0	1 (0.1)	0	1 (0.1)	0
Gastrointestinal Disorders	3 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	4 (0.1)	0
General Disorders and Administration 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
Non-cardiac Chest Pain	0	1 (0.2)	0	0	1 (<0.1)	0
Infections and Infestations	4 (0.3%)	2 (0.5)	7 (0.5%)	3 (0.3%)	12 (0.4%)	1 (0.2%)
Appendicitis	0	0	0	1 (0.1)	1 (<0.1)	0
Bronchitis	0	0	1 (0.1)	0	1 (<0.1)	0
Clostridial Infection	0	0	1 (0.1)	0	1 (<0.1)	0
Diverticulitis	0	1 (0.2)	0	0	1 (<0.1)	0
Erysipelas	0	0	0	1 (0.1)	1 (<0.1)	1 (0.2)
Gastroenteritis	0	0	1 (0.1)	0	1 (<0.1)	0
Hepatitis A	0	0	1 (0.1)	0	1 (<0.1)	0
Post Procedural Infection	0	0	1 (0.1)	0	1 (<0.1)	0
Pyelonephritis Acute	0	1 (0.2)	0	0	1 (<0.1)	0
Sepsis	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	0
Urinary Tract Infection	0	0	0	1 (0.1)	1 (<0.1)	0
Injury, Poisoning	3 (0.2%)	0	3(0.2)	4 (0.4)	7 (0.3)	1 (0.2)

and Procedural Complications						
Cerebral Hemorrhage Traumatic	0	0	0	1 (0.1)	1(<0.1)	0
Fall	0	0	0	1 (0.1)	1(<0.1)	1(0.2)
Humerus Fracture	0	0	1 (0.1)	0	1(<0.1)	0
Limb Injury	0	0	1 (0.1)	0	1(<0.1)	0
Open Wound	0	0	1 (0.1)	0	1(<0.1)	0
Post Procedural Hematoma	0	0	0	1 (0.1)	1(<0.1)	0
Radius Fracture	0	0	1 (0.1)	0	1(<0.1)	0
Investigations	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Cardiovascular Evaluation	0	0	0	1 (0.1)	1(<0.1)	0
Hepatic Enzyme Increased	0	0	1 (0.1)	0	1(<0.1)	0
Liver Function Test Abnormal	0	1 (0.2)	0	0	1(<0.1)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1)	0	4 (0.3)	1 (0.1)	5 (0.2)	1 (0.2)
Cervical Spinal Stenosis	0	0	1 (0.1)	0	1(<0.1)	0
Lumbar Spinal Stenosis	0	0	0	1 (0.1)	1(<0.1)	0
Osteoarthritis	0	0	1 (0.1)	0	1(<0.1)	0
Rotator Cuff Syndrome	0	0	1 (0.1)	0	1(<0.1)	0
Spinal Column Stenosis	0	0	1 (0.1)	0	1(<0.1)	0
Neoplasms Benign, Malignant	1 (0.1)	1 (0.1)	3 (0.2)	3 (0.3)	7 (0.3)	1 (0.2)
Bladder Cancer	0	0	0	1 (0.1)	1(<0.1)	0
Bowen's Disease	0	0	0	1 (0.1)	1(<0.1)	0
Breast Cancer	0	1 (0.2)	0	0	1(<0.1)	0
Colon Cancer Metastatic	0	0	0	1 (0.1)	1(<0.1)	0
Recurrent Lung Carcinoma	0	0	0	1 (0.1)	1(<0.1)	0
Malignant Melanoma	0	0	1 (0.1)	0	1(<0.1)	0
Lymph Node Metastases	0	0	1 (0.1)	0	1(<0.1)	0

Prostate Cancer	0	0	2 (0.1)	2 (0.1)		0
Nervous System Disorders	7 (0.5)	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.4)
Pregnancy, Puerperium, Perinatal	0	0	1 (0.1)	0	1 (<0.1)	0
Pregnancy	0	0	1(0.1)	0	1(<0.1)	0
Psychiatric Disorders	2 (0.1)	0	1 (0.1)	0	1 (<0.1)	0
Bipolar Disorder	0	0	1 (0.1)	0	1 (<0.1)	0
Renal and Urinary Disorders	1 (0.1)	0	3 (0.2)	3 (0.3)	6 (0.2)	0
Calculus Ureteric	0	0	0	1 (0.1)	1 (<0.1)	0
Calculus Urinary	0	0	0	1 (0.1)	1 (<0.1)	0
Hematuria	0	0	0	1 (0.1)	1 (<0.1)	0
Nephrolithiasis	0	0	1(0.1)	0	1 (<0.1)	0
Renal Failure Acute	0	0	1(0.1)	0	1 (<0.1)	0
Reproductive System and Breast Disorders	0	0	0	1 (0.1)	1 (<0.1)	0
Rectocele	0	0	0	1 (0.1)	1 (<0.1)	0
Vaginal Erosion	0	0	0	1 (0.1)	1 (<0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0	0	0	0	1 (0.2)
Surgical and Medical Procedures	3 (0.2)	0	2 (0.1)	2 (0.2)	4 (0.1)	1 (0.2)
Angioplasty	0	0	1 (0.1)	0	1 (<0.1)	0
Bunion Operation	0	0	0	2 (0.2)	1 (0.1)	0
Gastric Banding		0	1 (0.1)	0	1 (<0.1)	0
Vascular Disorders	1 (0.1)	1 (0.2)	1 (0.1)	0	2 (0.1)	1 (0.2)
Hypertensive Crisis	0	0	1 (0.1)	0	1 (<0.1)	0
Orthostatic Hypotension	0	1 (0.2)	0	0	1 (<0.1)	0

Source: Table 5.6.3.1, ISS, page 6950

Reviewer's Comments: The higher exposure in females compared to males is not reflected in an increase of SAE's in females as opposed to males.

In the Phase 3 EU/NA Study Population, there are several review issues based on the preceding table of SAEs:

- 1. There is a small difference in incidence of atrial fibrillation as an SAE in the mirabegron group over the placebo group. This difference is too small in my opinion to be clinically and statistically distinguishable from the placebo result.*
- 2. There are a total of three reports of urolithiasis as an SAE in the mirabegron group versus none in the placebo group. We cannot discern when the stones that became symptomatic (renal colic) were formed and therefore attribution of new stone formation is problematic. Mention of renal colic may be appropriate as an AE term in labeling.*
- 3. There appears to be a small difference of infections noted in patients dosed with 50 mg of mirabegron (7) versus placebo (4). These infections are single occurrences for 7 preferred terms for mirabegron 50 mg and are single occurrences for 4 preferred terms for placebo subjects. There was no urinary tract infection noted in patients receiving mirabegron 50 mg. I cannot conclude that this indicates an increased propensity for infections in association with mirabegron use.*
- 4. The report of “hypertensive crisis” was evaluated and thus far, does not appear to meet criteria for “hypertensive crisis” and instead should be classified as hypertension.*
- 5. There is a difference between mirabegron and placebo in total number of neoplasms reported as an SAE when a variety of differing tumors, each reported by 1 patient, are added together. This difference is driven by results in one study (178-CL-047), and mostly by the 100 mg group. When these cases were analyzed, most were found to be pre-existing.*
- 6. There are several isolated reports of SAE traumatic injuries in mirabegron treated patients versus none with placebo. Additional information was obtained from the Sponsor regarding each case. The results were analyzed. Within the three pivotal studies, the incidence of preferred terms such as fall, fracture or injury were tabulated. The number of these events for the placebo subjects was 2, for the mirabegron 50 mg subjects was 3, for the mirabegron 100 mg subjects was 2 and for tolterodine subjects it was 3. The results were similar in the long term safety study: 4 events for that mirabegron 50 mg group, 3 events for the mirabegron 100 mg group and 3 events for the tolterodine group. There was no indication of decreased attention, concentration, obtundation or awareness associated with these events except for one subject (#3140-1831) who was injured in association with alcohol ingestion.*

Within Study 178-CL-049, the 52-week long-term safety study, there was not an increased incidence of atrial fibrillation in the tolterodine group compared to the mirabegron group (0.4% versus 0.1% respectively). There were four reports of liver function abnormalities (0.1 %) in the mirabegron group versus none for tolterodine. Within the SOC of Musculoskeletal and Connective Tissue Disorders, 8 (0.5%) of mirabegron patients versus 2 (0.2%) of tolterodine patients reported SAEs. Within the Neoplasms, Benign and Malignant (including cysts and polyps) SOC, in the mirabegron 50 mg dose group, 1 (0.1%) reported a neoplasm SAE, and 11 (1.3%) reported a neoplasm SAE in the mirabegron 100 mg arm. In the tolterodine comparator group, 4 (0.5%) reported a neoplasm SAE. There was one report of hypertension in each of the mirabegron treatment groups (0.1%) versus none in the tolterodine group.

Table 70: SAE (>= 2 patients in the Total Mirabegron Group), EU/NA Long-Term Controlled Population

MedDRA (v12.1) SOC PT (preferred term), n (%) of patients	Mirabegron			Tolterodine ER 4 mg (n=812)
	50 mg (n=812)	100 mg (n=820)	Total (n=1632)	
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 Hemorrhage	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%)
Abcess 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 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	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
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 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

Source: Table 42, ISS, page 131

Reviewer's Comments:

- Three 50 mg mirabegron patients were noted to have atrial fibrillation in Study 178-CL-049. The reader is referred to the detailed narratives in Study 049 report. In brief, patient 1681-6947 is 82 years old and sustained atrial fibrillation in association with pneumonia. Patient 3105-2977 (50 mg) developed atrial fibrillation in association with congestive heart failure. Patient 3433-1273 (50 mg) developed atrial fibrillation. She was hyperthyroid but lab values indicated good control. In this case only, a causal association with mirabegron cannot be ruled out.*
- Three patients in the mirabegron 100 dose arm had reports of abnormalities of liver function tests. Patient 1667-1602 had elevations of liver enzymes in association with pancreatitis and cholelithiasis. Patient 2037-0516 had liver function test abnormalities in association with a hypersensitivity reaction (hemolytic anemia). Patient 1630-6655 had elevated liver function tests and a liver biopsy compatible with autoimmune hepatitis or drug reaction. The patient has an autoimmune history and was taking ibuprofen.*
- Patient 3019-0364 (50 mg) reported hypertension but the blood pressure on the day reported was not different from baseline levels. Patient 1630-7319 (100 mg) was subject to stress at the time he was reported hypertensive.*
- There were two cases of intestinal abscess. In patient 3030-1541 (50 mg), a diverticular abscess was noted in the setting of pre-existing diverticulitis. The patient sustained a CVA in the postoperative period. Patient 1630-6655 (100 mg) sustained an intestinal abscess in association with a diverticular perforation.*
- With respect to CVA, patient 3117-3170 (50 mg) had multiple vascular risk factors. Patient 3030-1541 was in the post operative period. Patient 1656-7207 (50mg) had cardiac and neurologic risk factors for CVA.*
- With respect to gastrointestinal disorders, Patient 2035-8053 (50 mg) had ongoing peptic ulcer disease aggravated by acetylsalicylic acid use resulting in erosive gastritis and upper GI hemorrhage. Patient 3016-1796 (100 mg) sustained gastritis in association with NSAID use for lumbar radiculopathy.*
- The incidence of neoplasms reported as SAEs is greater for mirabegron 100 mg compared to mirabegron 50 mg and to tolterodine ER 4 mg. This issue is discussed in detail in the individual study review for Study 178-CL-049 and in the section entitled Adverse Events of Interest. Though most, and perhaps all, these cases were likely pre-existing conditions, the difference between groups is notable and remains of some concern.*

7.3.3 Dropouts and/or Discontinuations

The EU/NA OAB 12-week Phase 3 Population studies included 4611 patients (2736 mirabegron, 1380 placebo and 495 tolterodine patients) who took at least one dose of double-blind study medication. In the EU/NA OAB 12-week Phase 3 Population, disposition and reasons for discontinuation of study drug were similar for all treatment groups. A total of 2429/2736 (88.8%) mirabegron, 1205/1380 (87.3%) placebo and 445/495 (89.9%) tolterodine patients completed the double-blind treatment period, while 307/2736 (11.2%) mirabegron, 175/1380 (12.7%) placebo and 50/495 (10.1%) tolterodine patients discontinued study drug. The most common primary reasons for discontinuation of study drug were AE (mirabegron: 106/2736 [3.9%]; placebo: 45/1380 [3.3%]; tolterodine: 24/495 [4.8%]) and withdrawal of consent (mirabegron: 93/2736 [3.4%]; placebo: 59/1380 [4.3%]; tolterodine: 9/495 [1.8%]).

The most common TEAEs (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%]). 0.1 % of mirabegron patients discontinued secondary to atrial fibrillation or palpitations as did similar percentage in the placebo group. 4 (0.1%) mirabegron patients discontinued due to tachycardia versus none in the placebo group. Abnormal liver function tests resulted in discontinuation in 3 (0.1%) mirabegron patients versus 1 (0.1%) placebo patient. Skin rash was reported in 2 (0.1%) of mirabegron patients leading to discontinuation versus 0 for placebo. “Hypertensive crisis” was reported in 2 (0.1%) mirabegron 50 mg subjects.

Table 71: EU/NA 12 Week Phase 3 Study Population TEAE Leading to Discontinuation by SOC where Mirabegron Total Group Exceed

System Organ Class	Placebo N=1380	Total Mirabegron N=2736	Key Driver(s) Preferred Term (n>1)
Overall n (%)	46 (3.3)	104 (3.8)	
Cardiac Disorders	3 (0.2)	13 (0.5)	Atrial fib (3 vs 1) Palpitations (3 vs 1) Tachycardia (4 vs 0)
General Disorders & Administrative Site Conditions	6 (0.4)	15 (0.5)	Edema Peripheral (3 vs 1) Pyrexia (2 vs 0)
Injury, Poisoning, Procedural Complications	0	2 (0.1)	
Investigations	2 (0.1)	11 (0.4)	ALT increased (3 vs 1) AST increased (3 vs 1)

			Bili increased (2 vs 1) Liver Test Abnormal (2 vs 0)
Musculoskeletal and Connective Tissue Disorders	4 (0.3)	4 (0.4)	
Pregnancy, Puerperium and Perinatal Conditions	0	1 (<0.1)	
Renal and Urinary Disorders	2 (0.1)	5 (0.2)	
Skin and Subcutaneous Disorders	2 (0.1)	12 (0.4)	
Vascular Disorders	2 (0.1)	8 (0.3)	Hypertension (6 vs 2) Hypertensive Crisis (2 vs 0)

Source: Table 5.8.3.1 ISS

Reviewer's Comments: In the Phase 3 EU/NA Study Population, relevant to the preceding table of discontinuations due to SAEs:

- 1. The proportion of discontinuations due to liver function abnormalities are greater in the mirabegron group than the placebo group. Three mirabegron subjects had mild elevations of LFTs (3312-3435[046], 2252-8275[047] and 2053-7047[079]). One of these patients had recently started rosuvastatin. In all three cases, improvement of liver enzyme levels was noted upon discontinuation of the study medication.*
- 2. Discontinuations due to "hypertension" are greater in the mirabegron group compared to the placebo group. There are also two reports of "hypertensive crisis" leading to discontinuation. These two cases (3028-2466[046] and 3086-1834[046]) were analyzed carefully and neither met criteria for hypertensive crisis. These two cases are classified by this reviewer as exacerbations of pre-existing hypertension (Patient 3028-2466 came into study with poorly controlled hypertension). There were additional cases of pre-existing hypertension with worsening (1667-7013[074], 1625-6505[047], 2252-8275[047], 2225-7773[047] and 2185-7652[047]. Patient 2038-70286[074] came into study with poorly controlled hypertension. No case of new onset hypertension resulted in discontinuation.*
- 3. Four mirabegron patients discontinued secondary to or in association with atrial fibrillation. Patient 2179-7843[047] had a history of hypertension, but had atrial fibrillation temporally related to mirabegron use. Patient 3225-2443[046] had multiple cardiac risk factors. Patient 3014-2243[046] sustained atrial fibrillation in the setting of a repeat episode of heart failure. Patient 1534-72081[074] 50 mg developed atrial fibrillation. The patient had a history of hypothyroidism with euthyroid status on treatment.*
- 4. There were four events of tachycardia in mirabegron patients. Patient 3132-71820(074) was randomized to mirabegron 25 mg and on Day 1, dizziness and tachycardia were reported. The patient had previous tachycardia that*

ended on Day -4(pulse 106 bpm on Day -4). Patient 2189-6590[047] was randomized to mirabegron 100 mg and sustained supraventricular tachycardia of 189 bpm in the absence of documented ischemia but with a history of coronary vessel disease. Patient 3281-1373[046] randomized to mirabegron 50 mg reported tachycardia and dyspnea on Day 51. Vital signs for this event are not available. Patient 3011-1858[046] randomized to mirabegron 100 mg reported tachycardia and nervousness on Day 23. There are no available vital signs for that day. Tachycardia may be associated with mirabegron use. .

- 5. There were three events of palpitations noted in mirabegron patients. Patient 0047-72204[074] had a past history of nausea and palpitations. On Day 16, she required medication for nausea and discontinued on Day 17 with nausea and palpitations. The patient was chronically taking levothyroxine and albuterol. No vital signs provided for Day 17. Patient 3195-1620 [046] randomized to mirabegron 100 mg on Day 27 was found to have a pulse of 92-102 bpm. On Day 56 she was discovered to be hyperthyroid. Patient 2015-7713[047] was randomized to mirabegron 100 mg. On Day 57, the adverse event of palpitations was reported. No pulse rates or ECG for Day 57 were available. ECG at screening was normal. Palpitations may be associated with mirabegron use.*
- 6. The proportion of discontinuations due to Skin and Subcutaneous adverse events is greater in the mirabegron group compared to placebo. Although no skin-related adverse event Preferred Term was reported in greater than 1 patient, there were multiple, single terms (n=5) possibly indicative of an allergic or hypersensitivity phenomenon.*

In the EU/NA Long-term Controlled Population, one or more TEAEs 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 TEAEs (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%]). Palpitations were noted in 2 (0.2%) of mirabegron 100 mg patients. Fatigue was a reason for discontinuation in 3 (0.4%) of mirabegron 100 mg subjects. Abnormal liver function tests were a discontinuation reason in 2 (0.2%) of mirabegron 100 mg patients and 0 mirabegron 50 mg patients. Six (0.4%) mirabegron 100 mg patients, and four (0.5%) mirabegron 50 mg patients discontinued secondary to hypertension, versus 3 (0.4%) tolterodine patients. The increased incidence of neoplasms has been discussed under SAEs.

Table 72: EU/NA Long Term Controlled Population TEAE Leading to Discontinuation by SOC where Total Mirabegron Group Exceeds Tolterodine ER 4 mg

System Organ Class	Tolterodine ER 4 mg N=812	Total Mirabegron N=1632	Key Driver(s) Preferred Term (n>1)
Overall n (%)	46 (5.7)	98 (6.0)	
General Disorders & Administrative Site Conditions	2 (0.2)	9 (0.6)	Fatigue (4 vs 1) Pain (2 vs 0)
Infections and Infestations	3 (0.4)	8 (0.5)	
Injury, Poisoning, Procedural Complications	1 (0.1)	5 (0.3)	
Neoplasms Benign, Malignant	1 (0.1)	7 (0.4)	Lung neoplasm malignant (2 vs 0) Prostate Cancer (2 vs 0)
Pregnancy, Puerperium and Perinatal Conditions	0	1 (0.1)	
Psychiatric Disorders	1 (0.1)	3 (0.2)	
Skin and Subcutaneous Disorders	1(0.1)	7(0.4)	Pruritis (2 vs 0) Rash (2 vs 1) Urticaria (2 vs 1)
Vascular Disorders	2 (0.1)	8 (0.3)	Hypertension (6 vs 2) Hypertensive Crisis (2 vs 0)

Source: Table 5.8.4.1 ISS

Reviewer's Comments: In the Phase 3 EU/NA Long-Term Population, relevant to the preceding table of discontinuations due to SAEs:

- 1. The hypertensive crises have already been discussed and found to be exacerbations of pre-existing hypertension. There are six additional reports of hypertension in Study 178-CL-49 in mirabegron subjects (2013-7601 [50mg], 3019-0634[50 mg], 3201-3611 [50 mg], 3292-2363 [50 mg], 3204-2675 [100 mg] and 3232-1080 [100 mg]. One of these patients had pre-existing labile hypertension and the remaining five had exacerbations of pre-existing hypertension. Exacerbation of pre-existing hypertension appears to be a possible adverse event in patients taking mirabegron.*
- 2. Skin and subcutaneous AEs are discussed in Section 7.4.6.1 Immunogenicity.*
- 3. The incidence of new malignancy events is discussed in Section 7.3.5.*
- 4. Four patients reported fatigue. One patient 3018-1328[100 mg] was being treated for hypothyroidism and developed anemia and fatigue on Day 221. Patient 3046-1668[100 mg] had a history of depression. Patient 3221-1175 [100 mg] had a history of hypothyroidism. The thyroid lab status was not*

included in the narrative. Patient 2013-7601 had a history of tiredness, somnolence and decreased libido.

7.3.4 Significant Adverse Events

The significant clinical adverse events are relatively few, and have been described in the two previous sections. There were no marked laboratory or physical examination abnormalities. There were no adverse events leading to or requiring an intervention disproportionate to one treatment group. Nonetheless, there were a number of safety concerns raised during drug development and these are discussed in the next section of this review.

7.3.5 Submission Specific Primary Safety Concerns

The submission specific safety concerns considered during drug development included the following items. These items were discussed with Sponsor throughout the program and they were addressed in various ways. This section provides more details regarding these concerns, including how they were addressed and/or resolved.

- Cardiovascular Safety: increases in blood pressure or worsening of pre-existing hypertension, atrial fibrillation, tachycardia, palpitations, QT prolongation (See Section 7.4.3 and 7.4.4).
- Hepatotoxicity (these adverse events are discussed under Hepatotoxicity, Section 7.4.2)
- Hypersensitivity reactions (these adverse events are discussed in Section 7.4.6)
- Neoplasms
- Glaucoma/increases intraocular pressure (Glaucoma and increased intraocular pressure are discussed below)
- Syncope, postural hypotension, and falls (these adverse events are discussed below)
- Urinary Tract event: UTI, retention, urolithiasis (see discussion below)
- Endocrine and metabolic disturbances (discussed in Section 7.4.2, Glucose Metabolism, Thyroid Function: no evidence endocrine dysregulation)
- Use of alpha 1-AR antagonists at baseline
- Use of systemic Beta blockers at baseline

Concomitant Use of Either Alpha1-AR antagonists or Systemic Beta Blockers at baseline:

It appears that patients using beta-blockers have similar efficacy results compared to patients not on ongoing beta-blockade medications. For more detail, the reader is referred to Section 6.1.7 and to Table 61. Evaluation of safety by use of systemic beta blockers at baseline was performed by Sponsor and no safety concerns were identified.

Reviewer's Comment: Since patients using beta-blockers may have increased comorbidities, it is important to know that the risk benefit of mirabegron still

appears favorable in my opinion. It is to be noted that the number of subjects may be too small to draw definitive conclusions.

With respect to use of alpha 1-AR antagonists at baseline, mirabegron 50 mg reduced the daily incidence of incontinence episodes similarly to the reduction in the overall study population. The reduction in the number of daily micturitions was less than that in the overall study population (-0.12 versus -0.55). For 100 mg dose of mirabegron the converse was true. The Sponsor analyzed the safety experience in these patients as follows:

In the EU/NA OAB 12-week Phase 3 Population, the use of alpha 1-AR antagonist at baseline was associated with a lower frequency of TEAE in the total mirabegron and placebo groups; this was also the case in the total mirabegron and tolterodine groups in the EU/NA Long-term Controlled Population. 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 and long-term controlled studies than without baseline use. Overall, the frequency of hypertension was generally higher among users of alpha 1-AR antagonists across treatment groups compared with nonusers. The frequency of cardiac arrhythmia, UTI, urinary retention, syncope, postural hypotension and falls, was generally similar among users of alpha 1-AR antagonists and nonusers. In patients with baseline use of alpha 1-AR antagonists (Yes category), the most common SAE in the total mirabegron group was chest pain (2/192 [1.0%]); no patients experienced chest pain with placebo or tolterodine. There was one patient who experienced an SAE of fall with concomitant use of mirabegron and alpha 1-AR antagonist. In patients with baseline use of alpha 1-AR antagonists (Yes category), the most common TEAE (by PT) leading to permanent discontinuation of study drug in the total mirabegron group was hypertension (2/192 [1.0%]); this TEAE did not lead to discontinuation of study drug in patients treated with placebo or tolterodine. Mean changes from baseline in PVR volume were also consistent among users and nonusers of alpha 1-AR antagonists. In the EU/NA Long-term Controlled Populations, no patients with baseline use of alpha 1-AR antagonists experienced a urolithiasis, seizure or glaucoma TEAE.

Reviewer's Comment: The numbers of subjects using alpha blockers may be too small to draw meaningful conclusions, but no safety concern is generated from the available data.

Glaucoma/Increased Intraocular Pressure (IOP):

Following the report of 2 serious adverse events (SAE) of glaucoma, the Sponsor conducted a systematic evaluation of adverse events reported as glaucoma or intraocular during the mirabegron clinical program. Subsequently, the FDA Division requested a dedicated study to assess the effect of mirabegron on IOP.

Study 178-CL-081 was a randomized, double-blind, placebo-controlled, non-inferiority study to assess the effect of mirabegron on IOP (intraocular pressure), a suprathreshold dose of mirabegron 100 mg (160 subjects) administered orally once daily for 8 weeks in healthy research subjects was non-inferior to placebo (160 subjects) for the primary endpoint of change from

baseline to day 56 in subject-average IOP, based on the non-inferiority limit of 1.5 mm Hg. IOP data from day 10 were concordant with day 56. The upper bound of the two-sided 95% CI for the difference in mean change from baseline to day 10 in subject-average IOP between mirabegron 100 and placebo was 0.3 mm Hg. No subject discontinued the study due to an increased IOP. Clinically significant increases in baseline IOP measurements occurred rarely and only in placebo-treated patients. Visual acuity and biomicroscopy data were generally unremarkable in this study with no reported glaucoma type AE.

In addition to conducting this dedicated IOP study, Astellas conducted a systematic evaluation of glaucoma-type AE in all completed clinical studies within the global mirabegron clinical development program which included 8752 patients (5863 mirabegron-treated patients) and 1000 mirabegron-treated healthy volunteers. The percent of patients with glaucoma events based on the expert panel assessment in the Global OAB 12-week Phase 2/3 Population was 0% [0/2142 patients; 95% CI: 0.00%, 0.17%] for placebo, < 0.1% [2/4414 patients; 95% CI: 0.01%, 0.16%] for mirabegron and 0% [0/958 patients; 95% CI: 0.00%, 0.38%] for tolterodine [Table 5.1]. In the EU/NA Long-term Controlled Population the percent of patients with glaucoma events based on the expert panel assessment was 0.1% [2/1632 patients; 95% CI: 0.01%, 0.44%] for mirabegron and 0.1% [1/812 patients; 95% CI: 0.00%, 0.68%] for tolterodine.

The Sponsor concluded that the evidence does not support an association between mirabegron and glaucoma. Study 178-CL-081 demonstrated that mirabegron at a supratherapeutic dose did not increase IOP after 8 weeks of treatment in healthy volunteers. In the view of the Sponsor, the available nonclinical and clinical data do not support an association between mirabegron and the observed events of glaucoma.

The Division of Transplant and Ophthalmologic Products has consulted with regard to the potential glaucoma (increased IOP) signal, the design of Study 178-CL-081 and the Sponsor's overall and final analysis. They concur with that analysis.

Reviewer's Comment: This resolves this review issue.

Neoplasms

An increased incidence of SAE reports of "neoplasms" in mirabegron subjects as compared to placebo and active comparator was noted in the Global Phase 2/3 population (12 week studies). The Sponsor undertook a program-wide evaluation 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 relative risk of new malignant events per patient years at risk in the Global Phase 2/3 population by the sponsor's calculation is 1.66 (95%CI [0.36, 7.65]) total mirabegron as compared to placebo and 1.83 (95% CI [0.74, 4.55]) for total mirabegron compared to all comparators. When non-melanoma skin cancers are excluded, the relative risk of cancer was 1.84 (95% CI [95% CI 0.51, 6.63]) for total mirabegron compared to all comparators (Table 13, page 60, Mirabegron and Neoplasms report). Study 178-CL-047 drove the neoplasm results in the 12-week, Phase 3 studies. Of the 10 new malignant events noted in the pooled total mirabegron population in the Global 12-Week Phase 2/3 population, 7 of those cases were in Study 178-CL-047 and 1 was in study 178-CL-074 and was a basal cell carcinoma. The new malignancy cases in Study 047 are analyzed in the review of Study 178-CL-047. 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 the US and Europe.

Reviewer's Comment: In the phase 3 pivotal studies, the vast majority of new malignant events (non-cutaneous) arose within 28 days of drug initiation and all were, my opinion, preexisting.

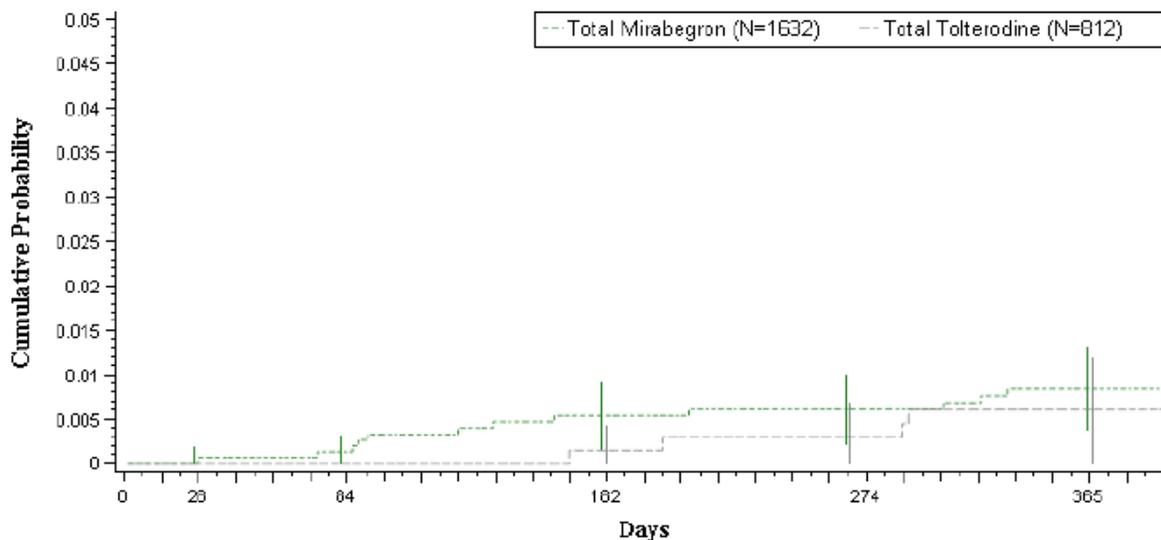
In the EU/NA Long-term Controlled Study 178-CL-049, the SAE reports within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) were higher in the mirabegron 100 mg treatment group compared with mirabegron 50 mg and tolterodine treatment groups. The reader is referred to a detailed discussion of these events presented in the review of Study 178-CL-049.

In Study 178-CL-049, there were three treatment arms: mirabegron 50 mg (n=812), mirabegron 100 mg (n=820) and tolterodine ER 4 mg (n=812). The incidence of SAE reports of neoplasm in each arm was 1 (0.1%) in the mirabegron 50 mg arm, 11 (1.3%) in the mirabegron 100 mg arm and 5 (0.7%) in the tolterodine arm. Patients in previous Phase 3 studies (178-CL-046 and 178 CL-047) and treatment naïve patients were allowed to enroll in Study 049. In the EU/NA Long-term Controlled Population, the overall frequency of patients with new malignant events was 12/1632 (0.74%) in the total mirabegron group (mirabegron only: 11/1395 [0.79%] and tolterodine/mirabegron (that is, patients who received tolterodine in the 12-week study followed by mirabegron in Study 049): 1/237 [0.42%]) compared with 4/812 (0.49%) in the total tolterodine group (tolterodine only: 3/444 [0.68%] and mirabegron/tolterodine (that is, patients who received mirabegron in the 12-week study followed by tolterodine in Study 049): 1/368 [0.27%]). The RR of new malignant events for the mirabegron only group compared with the tolterodine only group was 1.17 (95% CI: 0.31, 6.55). The RR of new malignant events for the total mirabegron group (mirabegron only and tolterodine/mirabegron groups) compared with the total tolterodine group (tolterodine only and mirabegron/tolterodine groups) was 1.50 (95% CI: 0.45, 6.38). A total of 21 events were reported in 16 patients across 7 tumors organs of origin.

The Sponsor's adjudication of the 16 neoplasm SAEs in Study 178-CL-049 resulted in 3 being excluded as pre-existing and 3 excluded as benign. When new malignant events were considered that were not SAEs 6 new malignant events were added. These were all non-melanoma skin cancers. The relative risk before the Sponsor's adjudication for new malignant events was 1.5

(95% CI 0.5, 6.4) for total mirabegron versus tolterodine. The relative risk after the Sponsor's adjudication for new malignant events was 1.5 (95% CI 0.5, 6.4) for total mirabegron versus tolterodine. The figure below provides a Kaplan-Meier analysis of new malignant events by the time to their report in Study 049.

Figure 6: Kaplan-Meier Curve Time to Onset New Malignant Adjudicated Events Study 178-CL-049



Number of Patients at Risk	Days					
	0	28	84	182	274	365
---Total Mirabegron	1632	1631	1515	1405	1325	1279
---Total Tolterodine	812	812	758	694	644	624

Study included: 178-CL-049.

Events with onset > 365 days were considered as having onset at day 365.

Source: Figure16, page 96, Neoplasm Research Report.

Reviewer's Comment: There is an unexplained difference between the mirabegron 100 mg group (a dose that is 2 to 4-fold higher than the to-be-marketed dose) and tolterodine in the incidence of new malignant events (including non-melanomatous skin malignancies). There is lack of a signal in the mirabegron 50 mg group. This issue was presented at an FDA Advisory Committee meeting, who recommended drug approval. For further analysis of individual neoplasms in Study 178-CL-049 and narratives, the reader is referred to the report of Study 178-CL-049.

On January 30, 2012, the Division received a completed Division of Oncology Products Consult. The consultation made the following observations based on questions submitted by the Division:

- Upon review and examination of the submitted adverse event dataset and the review of the study report on neoplasms identified during the trial, the consultant found that the number of neoplasms reported as an SAE was accurately reflected in the study report.
- The submitted narratives show that all the serious neoplasms, except for Case 3016-1796 (fibroma), were supported by pathological evidence and cannot be excluded. The consultant agreed with the Adjudication Committee's case by case analysis of neoplasms in Study 178-CL-049.
- The recommended dose for the proposed indication is 50 mg mirabegron once daily which had the lowest incidence of neoplasms in the three study arms.
- The consultant is not aware of a similar clinical situation in which the incidence of neoplasms was found responsive to a 2-fold increase in dose (50-100 mg mirabegron).
- While the 100 mg mirabegron dose once daily is not recommended in the draft product label, the increased number of neoplasms in the mirabegron 100 mg group was still of some concern.
- The consultant did not recommend pooling the data from the mirabegron 50 mg and 100 mg groups in Study 049 to compare with the control arm for the following reasons:
 - 5 of 11 neoplasm SAEs in the mirabegron 100 group were diagnosed within 12 weeks of study treatment and that 2 of the 11 diagnosed were diagnosed between Months 3-6 of the treatment initiation. The remaining 4 cases, including the case of fibroma, were found between months 6-12 of the trial. This is comparable to the time course of the neoplasms found in the tolterodine arm.
 - With the four 12-week Phase 3 trials of the product, a remarkable imbalance of malignancies was not found; however, the consultant notes that in the 1-year study 5 of 11 cases occurred within the first 12 weeks.
 - The detected neoplasms were heterogeneous in tissue of origin.
- There is no apparent relationship between prior exposure and neoplasm detection in Study 049. The significance of previous exposure to mirabegron, tolterodine, or placebo is difficult to estimate.
- The consultant did not find a remarkable imbalance in the incidence of neoplasms among the 4, 12-week, phase 3 studies (includes a non-NDA Japanese study) of the product.
- The consultant recommended no additional analyses. The consultant noted that any need for further studies could be discussed at the Advisory Committee meeting.

Reviewer's Comment: The gender distribution of the 17 neoplasm subjects is 5 male and 11 females which mirrors the sexual distribution of all subjects enrolled in Study 178-CL-049. Of the 17 neoplasm subjects, three were from the US, eight were from Germany, two were from France, two were from Sweden, and one was from Canada. The tumors represent the most common tumors occurring in most populations.

It is highly probable that all of the neoplasms noted in Study 178-CL-049 were pre-existing based on the known mechanisms of carcinogenesis and known length of time that tumors take to grow to a sufficient size to cause symptoms or permit detection. The increased incidence of non melanoma skin cancers is of note as skin lesions being external can be detected at earlier stages than cancers in other organs. There is no

common mechanistic or receptor data to implicate mirabegron as related to these cancers. It would seem reasonable to mention the incidence of neoplasms in labeling and to consider measures capable of monitoring for or investigating this issue further in the postmarketing period. Whether such postmarketing efforts are reasonable or feasible will require consultation with Office of Surveillance and Epidemiology at FDA as well as consultation with the Sponsor.

Urinary Tract Events: UTI, retention, urolithiasis

There was a small but consistent treatment difference in the proportion of UTIs in the mirabegron and tolterodine compared with the placebo groups, with a generally similar occurrence across mirabegron dose groups. In the Phase 3 Population, one or more UTI TEAE was reported by 99/2736 (3.6%) mirabegron, 34/1380 (2.5%) placebo and 15/495(3.0%) tolterodine patients (Table 6.3.1.2.1 ISS/SCS).

In the overall 12-week and the EU/NA Long-term Controlled populations, there were no differences in the frequency of UTIs between mirabegron and tolterodine. One or more UTI TEAE was reported in 143/1632 (8.8%) mirabegron patients (mirabegron 50 mg: 74/812 [9.1%]; mirabegron 100 mg: 69/820 [8.4%]) and 81/812 (10.0%) tolterodine patients. The most common Urinary TEAE (by PT) in the total mirabegron group were UTI (mirabegron: 93/1632 [5.7%]; tolterodine: 52/812 [6.4%]), cystitis (mirabegron: 28/1632 [1.7%]; tolterodine: 19/812 [2.3%]) and dysuria (mirabegron: 13/1632 [0.8%]; tolterodine: 4/812 [0.5%]). Consistent with a greater duration of observation, the frequency of UTI was higher in the long-term populations than in the 12-week populations.

Female patients, elderly patients and patients with a history of diabetes generally had higher frequencies of UTI; the frequencies were also higher in the mirabegron-treated patients than in placebo-treated patients.

The frequency of UTI TEAE was examined in the subgroup of male patients according to history of BPH. Although the rates of UTI were generally higher in male patients with BPH history compared with male patients without BPH history, the pattern of treatment comparisons between mirabegron, placebo and tolterodine is similar to that observed in the overall population, indicating that these patients are not at increased risk of UTI with mirabegron treatment. In the Phase 3 Population, one or more UTI TEAE in patients reporting BPH was 2/161 (1.2%) for placebo, 1/66 (1.5%), 3/157 (1.3%), and 3/104 (2.9%) for mirabegron 25 mg, 50 mg and 100 mg respectively and 6/331(1.8%) for tolterodine patients.

Reviewer's Comment: There is a modest increased incidence of UTI in mirabegron patients as compared to placebo.

There were no clinically meaningful differences between treatments groups in mean changes from baseline to any post baseline visit in PVR volume or in overall categorical shifts from baseline to post baseline PVR volume.

No AE of acute retention of urine were observed in mirabegron-treated patients in Studies 178-CL-047 and 178-CL-074, where patients at risk for acute retention of urine were not specifically excluded. One patient treated with placebo (Patient No. 178-CL-047, U00021856492) and one patient treated with mirabegron 50 mg in Study 047 (Patient No. 178-CL-046, 3018-1731) reported an SAE of acute retention of urine (LLT). This patient was a 59-year-old male patient treated with mirabegron 50 mg reported an SAE of acute urinary retention and UTI. This subject was taking tamsulosin. The patient had a transurethral and suprapubic bladder catheter placement for urinary retention. This patient discontinued due to the SAE of urinary retention on Day 48. He subsequently underwent a transurethral prostate resection on Day 70.

In the total mirabegron group, 2/4414 (< 0.1%) patients reported urinary retention based on TEAE criteria alone and 9/4414 (0.2%) patients had urinary retention based on PVR criteria alone (i.e., change from baseline of ≥ 150 mL); none of the mirabegron patients reported urinary retention based on both TEAE criteria and PVR criteria. In the placebo group, 7/2142 (0.3%) patients reported urinary retention based on TEAE criteria alone, 10/2142 (0.5%) patients had urinary retention based on PVR criteria alone. In the tolterodine group, 3/958 (0.3%) patients reported urinary retention based on TEAE criteria alone, 4/958 (0.4%) patients had urinary retention based on PVR criteria alone (i.e., change from baseline of ≥ 150 mL) and 1/958 (0.1%) patients had urinary retention based on both TEAE criteria and PVR criteria.

Reviewer's Comment: The incidences of retention in the Phase 3 studies are low and comparable between mirabegron and placebo (male and female). There was one male BPH subject who developed retention. The risk of retention with mirabegron is small as is the risk of retention with mirabegron as demonstrated in the dedicated urodynamics study, Study 178-CL-60.

In the EU/NA Long-term Controlled Population, one or more urinary retention TEAE was reported by 2/1632 (0.1%) mirabegron patients (mirabegron 50 mg: 1/812 [0.1%]; mirabegron 100 mg: 1/820 [0.1%]) and 3/812 (0.4%) tolterodine patients.

One patient treated with mirabegron 100 mg ([Patient No. 178-CL-049, 2203-0481], a 59-year-old female who was postoperative for severe lumbar spinal stenosis, reported urinary retention. The event (Day 184) occurred in association worsening paresthesia to the lower extremities and worsening urinary incontinence (Days 199). One patient treated with tolterodine reported the TEAE (by LLT) of acute retention of urine. Another patient treated with tolterodine [Patient No. 178-CL-049, 3232-2147], a 65-year-old male also experienced the TEAE (by LLT) of acute retention of urine. This patient had been taking mirabegron 50 mg in a phase 3 study. He had a history of LUTS since 2000 and was maintained on alfuzosin. On Day 31, he experienced retention with 2L of urine noted at catheterization. Ultimately the catheter was removed at Day 53 with PVR reported of 135 mL.

Reviewer's Comment: The long term use of mirabegron was associated with a very small incidence of retention which was less than that noted for tolterodine. In

this long term study, 3 males experienced retention and all 3 were in the tolterodine arm.

There were 3 subjects in the pivotal 12 week studies who experienced an SAE or an AE requiring discontinuation for renal colic. In the Phase 3 Population, one or more urolithiasis TEAE was reported in 8/4414 (0.2%) mirabegron and 1/2142 (< 0.1%) placebo patients, with no apparent mirabegron dose response; no patients treated with tolterodine reported a urolithiasis TEAE. The most common urolithiasis TEAE (by PT) in the total mirabegron group was nephrolithiasis (mirabegron: 6/4414 [0.1%]; placebo: 1/2142 [< 0.1%]; tolterodine: 0/958). Renal lithiasis was noted in 1/1380 (0.1%) of placebo subjects, 3/432 (0.7%) of mirabegron 25 mg subjects, 2/1375 mirabegron 0.1% of mirabegron 100 mg subjects and 6/2736 (0.2%) of tolterodine subjects. Ureteral calculus was noted in none of the placebo or mirabegron 25 mg subjects, 1 (0.1%) of mirabegron 50 mg subjects and 2 (0.2%) of mirabegron 100 mg subjects. No tolterodine patient reported the AE of ureteral calculus.

Reviewer's Comment: In the 3 month pivotal studies, it appears that there is a modestly increased incidence of reported nephrolithiasis events in mirabegron subjects, especially in the 25 mg group. It is not known if these stones were diagnosed incidentally or secondary to symptoms. In any case, without prior upper urinary tract imaging it is not possible to attribute their formation to mirabegron.

In the long-term study, the incidence of nephrolithiasis was similar between both doses of mirabegron and tolterodine. The incidence of renal colic was also similar between both doses of mirabegron and tolterodine.

Reviewer's Comment: While proteinaceous bladder calculus was noted at very high mirabegron doses in preclinical studies, no renal calculi were noted.

Syncope, Postural Hypotension, Falls and Seizures

In the OAB 12-week Phase 3 Population, one or more events of syncope, postural hypotension or falls were reported by 64/2736 (2.3%) mirabegron, 24/1380 (1.6%) placebo and 4/495 (0.8%) tolterodine patients, with no apparent mirabegron dose response. The majority of events were under the category of falls; one or more syncopal episodes was noted in 0.5% of mirabegron 25 mg patients (and lower syncope event rates at higher mirabegron doses). Postural hypotension was reported in one mirabegron 25 mg patient. Events of falls were more frequently reported in mirabegron 25 mg and 50 mg subjects compared to placebo, but not in the mirabegron 100 mg groups, and without apparent mirabegron dose response (see table below). The most common TEAEs (by PT) in the total mirabegron group under the category of falls were fall (8/2736; 0.3%), contusion (7/2736; 0.3%), hand fracture (4/2736; 0.1%) and limb injury (5/2336; 0.2%).

Table 73: Syncope, Postural Hypotension, Falls and Seizure Phase 3 Population

MedDRA	Placebo	Mirabegron	Tolterodine
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v12.1 (n%) of Patients	(n=1380)	25 mg (n=432)	50 mg (n=1375)	100 mg (n=929)	ER 4 mg (n=495)
Overall	24 (1.7)	16 (3.7)	32 (2.3)	16 (1.7)	4 (0.8)
Syncope	1 (0.1)	2 (0.5)	2 (0.2)	0	0
Postural Hypotension	0	1 (0.2)	0	0	0
Falls	23 (1.7)	13 (3.0%)	31 (2.3)	16 (1.7)	4 (0.8)
Seizure	0	0	0	0	0

Source: Table 6.6.1.2.1, ISS/SCS and Section 2.1.5.3 SCS page 80.

In the EU/NA Long-term Controlled Population, one or more TEAE of syncope, postural hypotension or falls were reported in 70/1632 (4.3%) mirabegron patients (mirabegron 50 mg: 40/812 [4.9%]; mirabegron 100 mg: 30/820 [3.7%]) and 41/812 (5.0%) tolterodine patients. The number of patients with events of syncope and postural hypotension was ≤ 2 in each treatment group; the majority of events were under the category of falls.

Table 74: Syncope, Postural Hypotension, Falls and Seizure EU/NA Long Term Population

MedDRA v12.1 (n%) of Patients	Mirabegron		Tolterodine ER 4 mg (n=812)
	50 mg (n=812)	100 mg (n=820)	
Overall	40 (4.9)	30 (3.7)	41 (5.0)
Syncope	2 (0.2)	0	2 (0.2)
Postural Hypotension	1 (0.1)	0	0
Falls	38 (4.7)	30 (3.7)	40 (4.9)
Seizure	0	0	0

Source: Table 6.6.1.3.1, ISS

In the EU/NA Long-term Controlled Population, one or more TEAE of syncope, postural hypotension or falls were reported in 70/1632 (4.3%) mirabegron patients (mirabegron 50 mg: 40/812 [4.9%]; mirabegron 100 mg: 30/820 [3.7%]) and 41/812 (5.0%) tolterodine patients. The number of patients with events of syncope and postural hypotension was ≤ 2 in each treatment group; the majority of events were under the category of falls. One or more TEAE under the category of falls was reported in 68/1632 (4.2%) mirabegron patients (mirabegron 50 mg: 38/812 [4.7%]; mirabegron 100 mg: 30/820 [3.7%]) and 40/812 (4.9%) tolterodine patients. Among the AE terms in this category, the most common TEAE (by PT) in the total mirabegron group was fall (mirabegron: 8/1632 [0.5%]; tolterodine: 5/812 [0.6%]). One or more syncope, postural hypotension or falls SAE was reported in 8/1632 [0.5%] mirabegron patients (mirabegron 50 mg: 4/812 [0.5%]; mirabegron 100 mg: 4/820 [0.5%]) and 2/812 (0.2%) tolterodine patients. All of these SAE were under the category of falls; there was no SAE of syncope or postural hypotension. None of the SAE led to permanent discontinuation of study drug. One or more syncope, postural hypotension and falls TEAE leading to permanent discontinuation of study

drug was reported in 4/1632 [0.2%] mirabegron patients (mirabegron 50 mg: 3/812 [0.4%]; mirabegron 100 mg: 1/820 [0.1%]) and 1/812 (0.1%) tolterodine patients. There were no patients who reported a syncope or postural hypotension TEAE leading to permanent discontinuation of study drug.

Reviewer's Comment: In the 12 week studies, there is an increase in incidence of reports when AE events of falls, hypotension and postural hypotension were pooled which is more frequent in mirabegron patients and specifically in mirabegron 25 mg patients. In the long term studies the incidences of these AEs between mirabegron and tolterodine subjects are similar. There is not a dose dependent increase of these AEs and if anything they, overall, are more frequent at a lower dose. These AEs are not indicative, in my opinion, of neurological or cardiac events which I believe was the reason the Sponsor placed this analysis in the submission. This reviewer further analyzed the incidence of SAEs and AEs resulting in discontinuation that were classified as falls fractures or injuries by dose group. In the 12 week population, two were reported in the placebo group, 3 were noted in the mirabegron 50 mg group and 2 were noted in the mirabegron 100 mg group. 3 such events were recorded in the tolterodine group. In the long term population, 4 incidents occurred in the mirabegron 50 mg group, 3 in the mirabegron 100 mg group, and 3 incidences were noted in the tolterodine group. In no case was there noted to be evidence of somnolence, decreased attention or lack of concentration except in 178-CL-049 patient 3140-831 who suffered injuries while under the influence of alcohol. This analysis raises no new safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the EU/NA OAB 12-week Phase 3 Population, the most common TEAE (by PT) reported in the total mirabegron group were hypertension (mirabegron: 200/2736 [7.3%]; placebo: 105/1380 [7.6%]; tolterodine: 40/495 [8.1%]), nasopharyngitis (mirabegron: 94/2736 [3.4%]; placebo: 35/1380 [2.5%]; tolterodine: 14/495 [2.8%]) and UTI (mirabegron: 83/2736 [3.0%]; placebo: 25/1380 [1.8%]; tolterodine: 10/495 [2.0%]). In the total mirabegron group, the maximum TEAE severity was mild for 25.0%, moderate for 17.6% and severe for 3.4% of patients. For placebo, the maximum TEAE severity was mild for 26.4%, moderate for 17.5% and severe for 3.8% of patients; for tolterodine the maximum TEAE severity was mild for 26.1%, moderate for 17.2% and severe for 3.4% of patients.

The table below illustrates the incidence of AEs $\geq 3.0\%$ in the total EU/NA Phase 3 12 Week Population:

Table 75: TEAE by PT (reported by $\geq 3.0\%$ in Total Mirabegron Group) EU/NA Phase 3 Population

MedDRA v12.1 PT, n (%) of patients	Placebo (n=1380)	Total Mirabegron			Tolterodine ER 4 mg (n=495)
		25 mg (n=432)	50 mg (n=1375)	Total (n=2736)	
Overall	658 (47.7)	210 (48.6)	647 (47.1)	1259 (46.0)	231 (46.7)
Hypertension	105 (7.6)	49 (11.3)	103 (7.5)	200 (7.3)	40 (8.1)
Nasopharyngitis	35 (2.5)	15 (3.5)	54 (3.9)	94 (3.4)	14 (2.8)
UTI	2.5(1.8)	18 (4.2)	40 (2.9)	83 (3.0)	10 (2.0)

Source: Table 23, SCS, page 57.

In the EU/NA Long-term Controlled Population, the most frequently reported TEAE (by PT) in the total mirabegron group were hypertension (mirabegron: 155/1632 [9.5%]; tolterodine: 78/812 [9.6%]), UTI (mirabegron: 93/1632 [5.7%]; tolterodine: 52/812 [6.4%]) and nasopharyngitis (mirabegron: 67/1632 [4.1%]; tolterodine: 25/812 [3.1%]).

Table 76: TEAE by PT (reported by $\geq 3.0\%$ in the Total Mirabegron Group) EU/NA Long-Term Controlled Population

MedDRA v12.1 PT, n (%) of patients	Total Mirabegron			Tolterodine ER 4 mg (n=812)
	50 mg (n=812)	100 mg (n=820)	Total (n=1632)	
Overall	485 (59.7%)	503 (61.3%)	988 (60.5%)	508 (62.6%)
Hypertension	75 (9.2%)	80 (9.8)	155 (9.5%)	78 (9.6%)
UTI	48 (5.9%)	45 (5.5%)	93 (5.7%)	52 (6.4%)
Nasopharyngitis	32 (3.9%)	35 (4.3%)	67 (4.1%)	25 (3.1%)
Headache	33 (4.1%)	26 (3.2%)	59 (3.6%)	20 (2.5%)
Back Pain	23 (2.8%)	29 (3.5%)	52 (3.2%)	13 (1.6%)

Source: Table 25, SCS, page 59.

Reviewer's Comment: Despite the incidences of "hypertension" reported as an AE, case by case reviews in each individual pivotal study review and in the long term study report reveals that new onset hypertension rarely occurs in mirabegron subjects versus placebo patients. There are small numbers of patients with existing hypertension or pre-hypertension who do experience an exacerbation of hypertension while taking mirabegron.

7.4.2 Laboratory Findings

Hematology

Hematology results for the EU/NA OAB 12-week Phase 3 Population were as follows:

Hemoglobin

The mean change from baseline to final visit for hemoglobin was 0.0, -1.0, -1.0, 0.0 and 0.0g/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [Table 70; ISS Table 7.1.2.1].

Hematocrit

The mean change from baseline to final visit for hematocrit (fraction) was -0.003, -0.007, -0.006, -0.004 and -0.006 in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [Table 70; ISS Table 7.1.2.1].

Platelets

The mean change from baseline to final visit for platelet counts was -3.0, -4.0, -2.0, -4.0, and -3.0 x 10⁹/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively. Changes were not clinically significant [Table 7.1.2.1].

Leukocytes (WBCs)

The mean change from baseline to final visit for leukocyte counts was 0.08, 0.10, 0.00, -0.10 and 0.17x 10⁹/L in the mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.2.1].

Neutrophils

The mean change from baseline to final visit for neutrophil/leukocytes (fraction) was -0.0020, , -0.0030, -0.0030, 0.0070 and 0.0010 in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.2.1].

Lymphocytes

The mean change from baseline to final visit for lymphocytes/leukocytes(fraction) was -0.0070, -0.0030, --0.0050, -0.0120 and -0.0095 in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.2.1]

Eosinophils

The mean change from baseline to final visit for eosinophil/leukocytes (fraction) was 0.0010, 0.0010, 0.0020, 0.0020 and 0.0020 in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.2.1].

In the EU/NA OAB 12-week Phase 3 Population, the frequency of patients with a categorical decrease from baseline to the lowest post baseline value for hemoglobin, hematocrit, and platelets were similar for placebo, mirabegron 25 mg and mirabegron 50 mg.

Shifts from baseline to the lowest post baseline leukocyte values represented a categorical decrease for 80/1311 (6.1%) placebo, 28/414 (6.8%) mirabegron 25 mg, 81/1319 (6.1 %) mirabegron 50 mg, 102/1249 (8.2%) mirabegron 100 mg, and 29/447 (6.1%) tolterodine patients [ISS Table 7.2.2.1].

With respect to Potentially Clinically Significant (PCS) hematology values, the frequency of patients whose hematology values met a PCS criterion was generally similar across treatment groups.

Table 77: Potentially Clinically Significant Hematology Values EU/NA Phase 3 Population

Laboratory Parameter n/n(%) of Patients	Criteria	Placebo (N=1380)	Mirabegron			Tolterodine ER 4 mg (N=495)
			25 mg (N=432)	50 mg (N=1375)	100mg (N=929)	
Erythrocytes (10 ¹² /L)	< 2.5 x10 ¹² /L	0/1334	0/ 418	0/1329	0/ 898	0/ 480
	> 7.0 x10 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	0/1329	0/898	0/480
Platelet Count (10 ⁹ /L)	<120 x 10 ⁹ /L	4/1330	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)	2/418 (0.5)	4/1327(0.3)	4/897 (0.4)	2/480 (0.4)
Leukocytes (10 ⁹ /L)	<2.5 x10 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)

Source: Table 7.3.3.1, ISS ADLB Labset

Reviewer's Comments: A review of the hematology results did not reveal any new safety concerns, in my opinion. A review of all abnormal platelet results was conducted in each of the individual study reviews. Most of the patients with a report of abnormal platelets had the report has a result of low platelet counts at study entry.

The following are the hematology Results for the EU/NA Long-term Controlled Population:

Hemoglobin and Hematocrit

In the EU/NA Long-term Controlled Population, for the hemoglobin and hematocrit parameters, there were no patterns of clinically significant change over time or across the mirabegron 50 mg, mirabegron 100 mg and tolterodine treatment groups [ISS Table 7.1.3.1].

Platelets

The mean change from baseline to final visit for platelet counts was -14.1, -13.6 and -14.5 x 10⁹/L in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.3.1].

Leukocytes (WBCs)

The mean change from baseline to final visit for leukocyte counts was -0.23, -0.23 and -0.13 x 10⁹/L in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [Table 71; ISS Table 7.1.3.1].

Neutrophils

The mean change from baseline to final visit for absolute neutrophil counts was -138.5, -102.6 and -57.1 x 10⁶/L in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. The baseline neutrophil counts were 4287, 4201 and 4105 for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. The mean changes from baseline were not statistically different between groups. Changes were not clinically significant [ISS Table 7.1.3.1].

Lymphocytes

The mean change from baseline to final visit for lymphocyte counts was -67.5, -100.5 and -53.0 x 10⁶/L in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.3.1].

Eosinophils

The mean change from baseline to final visit for absolute eosinophil counts was 1.3, -1.8 and 2.8 x 10⁶/L in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. Changes were not clinically significant [ISS Table 7.1.3.1].

In the EU/NA Long-term Controlled Population, the frequency of patients with a categorical decrease from baseline to lowest hemoglobin, hematocrit, platelet or leukocyte count value during treatment was similar across treatment groups [ISS Table 74, page 204].

Table 78: Potentially Clinically Significant Hematology Values, EU/NA Long-term Controlled Population

Laboratory Parameter 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 x10 ¹² /L	0/792	0/803	0/791
	> 7.0 x10 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%	1/702(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 x10 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

Source: Table 78, ISS, page 208

With respect to patients who met clinical thresholds (grade 2 and 3) for low lymphocyte (Grade 2 ≥ 500 to < 800 , Grade 3 ≥ 200 to < 1000) and low neutrophil counts (Grade 2 ≥ 1000 to < 1500 , Grade 3 ≥ 500 to < 1000), the frequency of patients with clinical threshold of grade 2 lymphocytes and neutrophils was higher for the mirabegron 100 mg group (25/800 [3.1%]) compared with the mirabegron 50 mg group (14/792 [1.8%]) or the tolterodine group (11/790 [1.4%]).

Hematologic SAEs that were reported included anemia (178-CL-049: 2035-8053 mirabegron 50 mg) in a 58 year old female with upper gastrointestinal bleeding, hemolytic anemia and thrombocytopenia (178-CL-049:2037-0516, mirabegron 100 mg), knee postoperative anemia (178-CL-049: 1534-0181, mirabegron 100 mg), and anemia (178-CL-045: P02471, placebo).

Reviewer's Comment: For a discussion of patients with platelet level of potential clinical concern (PCS) the reader is referred to the Study 178-CL-049 in this NDA review. Overall, the hematologic safety profile of 50 mg mirabegron is similar to that of tolterodine and raises no new safety concerns, in my opinion.

Chemistry Parameters

Liver Function Tests (Evaluation for Hepatotoxicity)

Based on preclinical studies, the liver was identified as a target organ of potential concern. The following discussion concerns hepatic chemistry changes in the three NDA pivotal studies and in the long-term safety population.

The following are liver function test results in the Pivotal Studies:

ALT

In the EU/NA OAB 12-week Phase 3 Population, the mean increase from baseline to final visit for ALT was 0.5, 1.4, -0.2, 1.2, and 0.8 in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively [ISS Table 7.1.1.2].

AST

The mean increase from baseline to final visit for AST was 0.1, -0.7, 0.3, 0.4 and 0.1 U/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively [ISS Table 7.1.1.2].

Other Hepatic Chemistries

The mean change from baseline to final visit in ALP (ranging from 0.3 U/L with mirabegron 100mg to 0.5 U/L with placebo), total bilirubin (ranging from 0.12 mcmol/L with placebo to 0.2 2 mcmol/L with mirabegron 50 mg and 0.38 mcmol/L with tolterodine) and GGT (ranging from 0.1 U/L with placebo to 0.2 with mirabegron 100 mg to 4.0 U/L with tolterodine). [ISS Table 7.1.1.2] were generally the same across treatment groups.

For scatter plots of maximum post-baseline value by baseline value and by paired hepatic laboratory parameter for ALT, AST, ALP and for total bilirubin in most cases, the maximum postbaseline value was ≤ 2 times the ULN.

Reviewer's Comment: These values are not indicative of a trend.

The following are liver function test results in the Long Term Controlled Population:

ALT

In the EU/NA Long Term Controlled Population, the mean increase from baseline to final visit for ALT was -0.3, -0.6. and -0.1 mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively [ISS Table 7.1.3.2].

AST

The mean increase from baseline to final visit for AST was -0.1, -0.4 and -0.4 U/L in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively [ISS Table 7.1.3.2].

Other Hepatic Chemistries

The mean change from baseline to final visit in ALP (ranging from -0.3 U/L with mirabegron 50 mg, -0.5 with mirabegron 100 mg and -0.9 for tolterodine), total bilirubin (ranging from 0.09 mcmol/L with mirabegron 50 mg, -0.13 and -0.19 mcmol/L with tolterodine) and GGT (ranging

from 0.4 U/L with mirabegron 50 mg, 0.0 with mirabegron 100 mg and 1.8 U/L with tolterodine) [ISS Table 7.1.1.2] were generally the same across treatment groups.

For scatter plots of maximum post-baseline value by baseline value and by paired hepatic laboratory parameter for ALT, AST, ALP and by total bilirubin in most cases, the maximum post baseline value was ≤ 2 times the ULN.

Reviewer's Comment: These values are not indicative of a trend.

The following data describe population shifts in liver function tests in the Phase 3 Pivotal Studies:

ALT

In EU/NA OAB 12-week Phase 3 Population, shifts from baseline to the highest post baseline ALT values represented a categorical increase for 147/1208 (12.2%) placebo, 47/378 (12.4%) mirabegron 25 mg, 137/1190 (11.5%) mirabegron 50 mg, 125/800 (15.6%) mirabegron 100 mg and 42/418 (10.0%) tolterodine patients [ISS Table 7.2.2.2].

AST

Shifts from baseline to the highest post baseline AST values represented a categorical increase for 79/1280 (5.3%) placebo, 34/398 (8.5%) mirabegron 25 mg, 105/1257 (8.4%) mirabegron 50 mg, 72/848 (8.5%) mirabegron 100 mg and 31/452 (6.9%) tolterodine patients [ISS Table 7.2.2.2].

Other Hepatic Chemistries

The frequency of increase from baseline to highest value for ALP, total bilirubin and GGT was generally similar across all treatment groups [ISS Table 7.2.1.2].

Reviewer's Comment: Despite slightly increased incidence of categorical shifts in AST in mirabegron groups compared to tolterodine, categorical shifts from baseline normal to high for liver function tests for mirabegron versus placebo in the 12-week studies were not overall indicative of a trend.

The following data describe population shifts in liver function tests in the EU/NA Long-term Controlled Population

ALT

In the EU/NA Long-term Controlled Population, shifts from baseline to the highest postbaseline ALT values represented a categorical increase for 106/678 (15.6%) mirabegron 50 mg, 92/704 (13.1%) mirabegron 100 mg and 72/700 (10.3%) tolterodine patients [ISS Table 7.2.3.2].

AST

Shifts from baseline to the highest post baseline AST values represented a categorical increase for 76/744 (10.2%) mirabegron 50 mg, 61/765 (8.0%) mirabegron 100 mg and 45/755 (6.0%) tolterodine patients [ISS Table 7.2.3.2].

Other Hepatic Chemistries

The frequency of increase from baseline to highest value for ALP, total bilirubin and GGT was generally similar across all treatment groups

Reviewer's Comment: Categorical shifts from baseline normal to high for mirabegron versus tolterodine were indicative of a possible trend of increase of ALT and AST for mirabegron versus tolterodine in Study 049.

The following data describe Potentially Clinically Significant (PCS) liver function test abnormalities in the EU/NA 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, 326 or 5.5% of patients experienced a hepatic chemistry value that met a PCS criterion (> than 3X the ULN for ALT/AST); the frequency was similar across treatment groups and similar to the Global OAB 12-week Phase 2/3 Population. For ALT or AST, 1.3% of mirabegron patients and 0.7% of placebo patients experienced values > 3 x ULN. Within the pooled, 12 week, Phase 3 studies for ALT: 8/1335 (0.6%) of placebo subjects, 4/416 (1.0%) of mirabegron 25 mg subjects, 2/1328 (0.2%) of mirabegron 50 mg subjects, 8/895 (0.9%) of mirabegron 100 mg subjects and 6/480 (1.3%) of tolterodine subjects met PCS criteria.

In the EU/NA OAB 12-week Phase 3 Population, the patient-years of exposure was 295.5 years for placebo, 93.1 years for mirabegron 25 mg, 296.6 years for mirabegron 50 mg, 202.1 years for mirabegron 100 mg and 108.9 years for tolterodine. The frequency of PCS abnormalities in hepatic chemistry laboratory tests per patient-years of exposure was similar across treatment groups (fewer than one patient per 10 patient-years of exposure for each PCS abnormality).

Table 79: PCS Hepatic Single Chemistry Laboratory Parameters EU/NA Phase 3 Studies

Laboratory Parameter n/n(%) of Patients	PCS Criterion	Placebo (N=1380)	Mirabegron		Tolterodine ER 4 mg (N=495)
			25 mg (N=432)	50 mg (N=1375)	
ALT or AST	>3 x ULN	9/1335 (0.7)	4/418 (1.0)	6/1328 (0.5)	6/480 (1.3)
	>5 x ULN	2/1335 (0.1)	1/418 (0.2)	2/1328 (0.2)	3/480 (0.6)
	>10 x ULN	1/1135 (0.1)	1/418 (0.2)	0/1328	1/480 (0.2)
	>20 x ULN	1/1335 (0.1)	0/418	0/1328	0/480
ALT	>3 x ULN	8/1335 (0.6)	4/418 (1.0)	6/1328 (0.5)	6/480 (1.3)
	>5 x ULN	2/1335 (0.1)	1/18 (0.2)	2/1328 (0.2)	3/480 (0.6)

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	>10 x ULN	0/1335	1/418 (0.2)	0/1328	1/480 (0.2)
	>20 x ULN	0/1335	0/418	0/1328	0/480
AST	>3 x ULN	2/1335 (0.1)	1/418 (0.2)	6/1328 (0.1)	2/480 (0.4)
	>5 x ULN	1/1335 (0.1)	1/418 (0.2)	0/1328	0/480
	>10 x ULN	1/1335 (0.1)	0/418	0/1328	0/480
	>20 x ULN	1/1335 (0.1)	0/418	0/1328	0/480
Alk Phosph	>1.5 x ULN	2/1335 (0.1)	1/ 418 (0.2)	4/1328 (0.3)	2/480 (0.4)
Bilirubin	>1.5 x ULN	8/1335 (0.6)	0/418	10/1328 (0.8)	4/480 (0.8)
	>2 x ULN	2/1335 (0.1)	0/418	3/1328 (0.2)	2/480 (0.4)
GGT	> 100 U/L	33/1335 (2.5)	12/ 418 (2.9)	21/1328 (1.6)	19/480 (4.0)

Source: ISS Table 7.3.3.1

Reviewer's Comment: PCS single hepatic chemistry profile for mirabegron is similar to that of placebo patients, in my opinion for the 50 mg group and perhaps modestly increased for ALT and AST for the 25 mg mirabegron dose. The lack of a dose response is notable.

No patient met the PCS criteria based on multiple hepatic parameters in the Phase 3 pivotal studies. In the EU/NA OAB 12-week Phase 3 Population, time-to-event was similar across treatment groups for ALP > 1.5 x ULN, ALT > 3 x ULN, AST > 3 x ULN and total bilirubin > 1.5 x ULN. Onset of the rare hepatic adverse events that were reported was generally at 8 weeks (56 days) or later. In the EU/NA OAB 12-week Phase 3 Population, one or more hepatotoxicity TEAE was reported by 41/2736 (1.5%) mirabegron, 17/1380 (1.2%) placebo and 10/495 (2.0%) tolterodine patients (Using MedDRA [v12.1] SOC Hepatobiliary and Investigations search terms).

In the EU/NA OAB 12-week Phase 3 Population, 3 patients (one each in the mirabegron 25 mg (0.2%), mirabegron 50 mg (0.1%) and tolterodine (0.2%) groups) experienced a hepatotoxicity SAE (178-CL-074 Patient 1630-70462: mirabegron 25 mg, 178-CL-046 Patient 3312-3435: mirabegron 50 mg, and 178-CL-046 Patient 3401-3312: tolterodine). In the EU/NA OAB 12-week Phase 3 Population, one or more hepatotoxicity TEAE leading to permanent discontinuation of study drug was reported by 6/2736 (0.2%) mirabegron and 1/1380 (0.1%) placebo patients; no (0/495) tolterodine patients experienced a hepatotoxicity TEAE leading to permanent discontinuation of study drug.

In the EU/NA OAB 12-week Phase 3 Population, hepatotoxicity was reported as a TEAE for 41/2736 (1.5%) mirabegron patients; placebo: 17/1380 [1.2%]; tolterodine: 10 / 495 [2.0%]), from laboratory data for 42/2736 (1.5 %) mirabegron patients (placebo: 19/1380 [1.4 %]; tolterodine: 10/495 [2.0%]) and both as a TEAE and from laboratory data for 11/2736 (0.4 %) mirabegron patients (placebo: 5/1380 [0.4 %]; tolterodine: 5/495 [1.0 %]). Hepatotoxicity from laboratory data is defined as any patient meeting the PCS criteria for hepatic laboratory

parameters (ALT or AST > 3 x ULN or total bilirubin or ALP > 1.5 x ULN).

Table 80: Hepatotoxicity Phase 3 Studies

Hepatotoxicity Category n(%)	Placebo N=1380	Total Mirabegron N=2736	Tolterodine ER 4mg N=495
TEAE	17(1.2)	41 (1.5)	10/495 (2.0)
SAE	1 (0.7)	2 (0.7)	1 (0.2)
AE leading to discontinuation	1 (0.1)	6 (0.2)	0

Source: Table 6.8.1.3, Table 108, Table 7.1.2.2 ISS

Reviewer's Comment: In the Phase 3 studies, based on clinical or laboratory-based measures, no significant positive trend relating to hepatotoxicity appears to be present, in my opinion.

EU/NA Long-term Controlled Population

In the EU/NA Long-term Controlled Population, the frequency of PCS abnormalities in hepatic laboratory tests was low ($\leq 1.3\%$) and similar across treatment groups. Two patients ([Patient No. 178-CL-049, 3051-2649] and [Patient No. 178-CL-049, 2044-6398]) had ALT or AST > 10 x ULN. Patient 3051-2649 [mirabegron 50 mg] had normal transaminases on Day -22. On Day 22, ALT was 676 U/L and AST was 605 U/L. Patient completed study. By Day 175, the ALT was 27 U/L and the AST was 25 U/L. Patient U00020446398 [mirabegron 50mg] had normal transaminases on Day -16. By Day 29, the ALT and AST were 125 and 451 U/L, respectively. By Day 41, they were 45 and 47 U/L respectively. By Day 171, they were 19 and 26 U/L. The patient was then lost to followup.

Table 81: PCS Hepatic Chemistry Abnormalities, EU/NA Long-term Controlled Population

Laboratory Parameter n/n(%) of Patients	PCS Criterion	Mirabegron		Tolterodine ER 4 mg (n=812)
		50 mg (n=812)	100 mg (n=820)	
ALT or AST	>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	>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	7/791
AST	>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
Alk Phosph	>1.5 x ULN	3/791 (0.4)	3/803 (0.4)	6/791 (0.8)
Bilirubin	>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
GGT	> 100 U/L	27/792 (3.4)	23/803 (2.9)	24/791 (3.0)

Source: Table 92, ISS page 232

Only one patient (Patient No. 178-CL-049, 3353-1381) in the EU/NA Long-term Controlled Population had 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation [Table 94; ISS Table 7.4.4; Study 178-CL-049] – a phenomenon some refer to as meeting “Hy’s Law”. This is the same patient with ongoing viral hepatitis as an alternate etiology previously discussed in the Study 178-CL-049 narratives. No other patient had elevations of ALT, AST and bilirubin combined at various multiples of abnormal levels.

Categorical shifts for ALT from normal baseline to high occurred in 106/676 (15.6%) mirabegron 50 mg subjects, 92/704 (13.1%) of mirabegron 100 mg subjects and 72/700 (10.3%) of tolterodine subjects in Study 049.

In the EU/NA Long-term Controlled Population, one or more hepatotoxicity TEAE was reported by 36/1632 (2.2%) mirabegron patients (mirabegron 50 mg: 17/812 [2.1%]; mirabegron 100 mg: 19/820 [2.3%]) and 15/812 (1.8%) tolterodine patients (Using MedDRA [v12.1] SOC Hepatobiliary and Investigations search terms). In the EU/NA Long-term Controlled Population, a total of 3 patients, all in the mirabegron 100 mg group, reported a hepatotoxicity SAE; 2 experienced SAE of liver function test abnormal and one experienced GGT increased (Patient 2037-0516, Patient 1630-6655 and Patient 3367-2053 [GGT]). In the EU/NA Long-term Controlled Population, one or more hepatotoxicity TEAEs leading to permanent discontinuation of study drug was reported by 2/1632 (0.1%) mirabegron patients (mirabegron 100 mg: 2/820 [0.2%]) and 1/812 (0.1%) tolterodine patients).

In the EU/NA Long-term Controlled Population, hepatotoxicity was reported as a TEAE for 36/1632 (2.2%) mirabegron patients (tolterodine: 15/812 [1.8%]), from laboratory data for 37/1632 (2.3%) mirabegron patients (tolterodine: 14/812 [1.7%]) and both as a TEAE and from laboratory data for 19/1632 (1.2%) mirabegron patients (tolterodine: 7/812 [0.9%]).

Table 82: Hepatotoxicity Events Study 178-CL-049

Hepatotoxicity	Mirabegron	Mirabegron	Total(N=1632)	Tolterodine ER 4
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n (%)	50 mg N=812	100 mg N=820	Mirabegron	mg N=812
Overall	17 (2.1)	19 (2.3)	36 (2.2)	15 (1.8)
SAE	0	3 (0.4)	3 (0.2)	0
TEAE leading to Discontinuation	0	2 (0.2)	2 (0.1)	1 (0.1)

Source: Table 106, Table 6.8.3.4 ISS

Reviewer's Comment: In Study 049, the incidence of hepatic AEs and SAEs is slightly greater in mirabegron groups compared to the tolterodine group, but this is more apparent in the mirabegron 100 mg group, not the mirabegron 50 mg group. It is notable that categorical upward shifts in serum transaminases (largely in the range of >3-fold, but not higher) were also slightly greater in incidence for mirabegron compared with tolterodine in Study 049.

Two patients met Hy's law in the mirabegron development program.

Patient No. 178-CL-045, P00244, a 74-year-old woman treated with mirabegron 100 mg, reportedly had 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation associated with a probable drug hypersensitivity syndrome; this patient experienced the SAE of Stevens-Johnson syndrome [Section 6.5.7]. On day 24, the patient developed nasopharyngitis, and on days 24 and 25, took the over-the-counter drug Kyufu Gold (po) containing acetaminophen at her own discretion. Urticaria of the lower extremities occurred on day 26. Laboratory tests taken on day 37 revealed AST > 3 x ULN, ALT > 3 x ULN, total bilirubin > 2 x ULN and ALP > 1.5 x ULN; increased ALP (peak ~ 4 x ULN) in conjunction with elevated bilirubin indicated a mixed type pattern (hepatocellular and cholestatic) not an exclusively hepatocellular liver dysfunction (ALT > 3 x ULN; total bilirubin > 2 x ULN; ALP < 2 x ULN). A drug lymphocyte stimulation test appears to provides evidence of an allergic reaction to mirabegron.

Patient No. 178-CL-049, 3353-1381, a 67-year-old man treated with mirabegron 50 mg, had 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation, but had a history of chronic hepatitis B (+hepatitis A and C) and alcohol abuse. ALT, AST and total bilirubin were elevated throughout the study as well as in the prior study (Study 178-CL-046, where he received tolterodine). The patient also experienced a mild TEAE of hepatic enzyme increased (day 36), considered by the investigator as mild and not related to the study drug. On day 185, the patient had AST of 120 U/L (ULN = 39 U/L) and total bilirubin of 42.1 mcmol/L (ULN = 18.6 mcmol/L). The history of chronic hepatitis B and alcoholism was considered to be an alternate etiology. This patient was not listed as an SAE.

Reviewer's Comment: Both cases are confounded (Case 3353-1381 perhaps more so than Case P00244); however, a causal association of these events and mirabegron cannot be excluded.

An additional hepatic AE case of note is considered below:

Patient No 178-CL-049, 1630-6655, a 58 year old female treated with mirabegron 100 mg had on Day 57 an ALT of 448 and an AST of 286 with a bilirubin of 8.7 (within normal limits) on Days 36 and 80. A liver biopsy on Day 77 was compatible with autoimmune hepatitis or drug induced liver injury (DILI).

Reviewer's Comment: In the EU/NA 12-week Phase 3 Population, one mirabegron 25 mg, one mirabegron 50 mg and one tolterodine patient reported hepatic AEs. One of the mirabegron patients had a past history of increased LFTS, a drug use history and positive tests for hepatitis A, B, and C (176-CL-074:1630-70462: 25 mg). Patient 3312-3435 in Study 176-CL-046 (50 mg) had increased liver enzymes as an SAE. This patient had a previous history of liver enzyme elevations for approximately eight years prior to mirabegron use. The patient was using confounding medications. Peak ALT/AST levels were 63 and 50 U/L respectively. One other hepatic adverse event was observed with mirabegron in Phase 3, but, in this mirabegron patient (176-CL-046:3355 -341: 50 mg), this patient had just contracted hepatitis A.

3 mirabegron 100 mg patients in the EU/NA Long-term Controlled Population, reported a hepatic SAE (1630-6655, 2037-0516 and 3367-2053). All recovered or are in the process of recovering according to the Sponsor. There were three additional patients in the long term study not reported as SAEs but in whom clinically meaningful hepatic events were reported: 1 patient in the long-term study, 3353-1381, receiving mirabegron 50 mg and with pre-existing hepatic disease (hepatitis A, B, C) had LFT elevations meeting Hy's Law. This patient voluntarily withdrew at Day 201. The other two cases (Patient No. 178-CL-049, 3051-2649 and Patient No. 178-CL-049, 2044-6398 [both mirabegron 50 mg]) had a rise of the ALT and AST to 10 times ULN with return to normal or baseline levels in the long-term study were observed.

Two patients in the overall clinical program had 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation within the entire mirabegron clinical program; however, an alternative etiology was identified in each case. One of these patients, in the long-term study, was the patient with hepatitis A, B and C and experienced a 3-fold elevation of the transaminases along with a 2-fold elevation of bilirubin (baseline levels were 73 and 85 U/L for ALT and AST and 22.6 umol/L for bilirubin). He withdrew from study at Day 201. One mirabegron 100 mg long term study patient with an allergic history and mild transaminases at baseline had transaminase rises (never met Hy's Law). A liver biopsy was compatible either drug induced hepatic injury or autoimmune hepatitis. Another 100 mg mirabegron long term patient had liver enzyme elevations in association with a hypersensitivity reaction of hemolytic anemia. A fourth long-term mirabegron patient (100 mg) at end of study had elevation of transaminases and GGT. She had a previous history of transaminasemia.

Taken together, most of the significant hepatic AE cases occurred in the setting of pre-existing liver function abnormalities. Several occurred as part of an allergic phenomenon. There are perhaps one to three cases where there were hepatic enzyme elevations in the absence of such phenomena. The questions are thus raised as to whether

mirabegron played a role in a few clinically significant hepatic AEs, or whether there is a relationship between mirabegron and liver function tests abnormalities in the context of a hypersensitivity reaction. The data is sparse and precludes definitive conclusions in this area. Hypersensitivity reactions have been discussed in other parts of this review previously and will be re-considered in the Immunogenicity section below.

Other Laboratory Parameters

Creatinine and Other Analytes

In the EU/NA Phase 3 OAB Population, the proportion of patients with $\geq 15\%$, $\geq 30\%$, $\geq 50\%$ and $\geq 100\%$ increase in serum creatinine for placebo, mirabegron 25 mg and mirabegron 50 mg were similar. 3 patients in the mirabegron 25 mg dose group had a serum creatinine > 177 $\mu\text{mol/L}$ (PCS level). Elevations of creatinine to this level did not occur in any other dose group. In one of the patients, creatinine was normal at the preceding and the succeeding visit. One of the subjects entered the study with a baseline creatinine of 181 $\mu\text{mol/L}$. The third subject had normal creatinine levels until the end of study visit when the creatinine was noted to be 662 $\mu\text{mol/L}$. A repeat blood level in the emergency room was within normal limits.

Serum BUN, glucose, hemoglobin A_{1c}, calcium, urate, albumin, lactate dehydrogenase, and protein were searched for the incidence of parameters exceeding the PCS levels by dose group. More patients in the 50 mg (69/1328[5.2%]) and 100 mg mirabegron (49/898[5.5%]) dose groups had PCS levels of lactate dehydrogenase than in the placebo (50/1135[3.7%]) and mirabegron 25 mg (15/418[3.6 %]) dose groups. In the tolterodine dose group 25/480[5.2%] had PCS values for lactate dehydrogenase.

Reviewer's Comment: The clinical significance of the increased PCS proportions of lactate dehydrogenase levels in the 50 and 100 mg mirabegron dose groups is unknown.

In the EU/NA Long-term OAB Safety Population, the proportion patients with $\geq 15\%$, $\geq 30\%$, $\geq 50\%$ and $\geq 100\%$ increases in creatinine for placebo, mirabegron 50 mg and tolterodine mg were similar. The table below illustrates the incidence of PCS levels for other chemistry analytes.

Table 83: PCS Abnormalities in Laboratory Tests, EU/NA Long-term Controlled Populations

Laboratory Parameter n/n(%) of Patients	PCS Criterion	Mirabegron		Tolterodine ER 4 mg (n=812)
		50 mg (n=812)	100 mg (n=820)	
Creatinine (mcmol/L)	>177 mcmol/L	0/792	0/803	1/791 (0.1%)
BUN (mmol/L)	>12.5 mmol/L	3/792 (0.4%)	7/803 (0.9%)	8/791 (1.0%)
Sodium (mmol/L)	<125 mmol/L	0/792	0/803	0/791
	>150 mmol/L	2/792 (0.3%)	1/803 (0.1)	5/791 (0.6)
Potassium (mmol/L)	<3.1 mmol/L	1/791 (0.1%)	3/803 (0.4%)	1/791 (0.1%)
	>5.6 mmol/L	14/791 (1.8%)	5/803 (0.6%)	4/791 (0.5%)
Calcium (mmol/L)	< 1.75 mmol/L	0/791	0/803	1/791 (0.1%)
	> 3.00 mmol/L	0/791	0/803	1/791 (0.1%)
Urate (mcmol/L)	>535 mcmol/L	4/792 (0.5%)	9/803 (1.1%)	7/791 (0.9%)
LDH (U/L)	>250 U/L	32/792 (4.0%)	25/803 (3.1%)	28/791 (3.5%)
Albumin (g/L)	< 26 g/L	0/792	0/803	1/791 (0.1%)
	> 60 g/L	0/792	0/803	0/791
Protein (g/L)	< 50 g/L	0/792	0/803	1/791 (0.1%)
	>100 g/L	0/792	0/803	1/791 (0.1%)
Glucose	<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)
Hgb A1C	>0.08 fraction	15/ 792 (1.9%)	15/ 803 (1.9%)	11/ 792 (1.4%)

Sources: ISS Table 7.3.4.1 and Table 124 ISS page 268.

Reviewer's Comment: Aside from modestly increased incidences of PCS glucose, there are no significant differences between mirabegron 50 and 100 mg doses and tolterodine. The effect on glucose metabolism was investigated by Sponsor and determined to be not clinically significant. This is discussed in more detail below.

Glucose Metabolism Laboratories

In the EU/NA OAB 12-week Phase 3 Population, the frequency of hypoglycemia was reported by 0/2736 (0.0 %) mirabegron, 1/1380 (0.1 %) placebo and 0/495 (0.0%) tolterodine patients [ISS Table 6.11.1.2]. No patient reported a hypoglycemic SAE or hypoglycemic TEAE leading to permanent discontinuation of study drug.

In the EU/NA OAB 12-week Phase 3 Population, one or more hyperglycemia TEAE was reported by 25/2736 (0.9%) mirabegron, 13/1380 (0.9%) placebo and 3/495 (0.6%)

tolterodine patients. 2/1380 placebo patients (0.1%), 0/432 mirabegron 25 mg patients, 5/1375 mirabegron 50 mg patients, 4/929 mirabegron 100 mg patients and 0/495 tolterodine patients reported hypoglycemia (ISS Table 6.10.1.2).

In the EU/NA Long-term Controlled Population, one or more hyperglycemia TEAE was reported by 30/1632 (1.8%) mirabegron patients (mirabegron 50 mg: 16/812 [2.0%]; mirabegron 100 mg: 14/820 [1.7%]) and 13/812 (1.6%) tolterodine patients.

In the Global OAB 12-week Phase 2/3 Population [ISS Table 6.10.2.1], the EU/NA OAB 12-week Phase 3 Population [ISS Table 6.10.2.2], and the EU/NA Long-term Controlled Population [ISS Table 6.10.2.3], no patients reported a hyperglycemia SAE. In the EU/NA OAB 12-week Phase 3 Population, Patient 178-CL-074: 3032-72997 permanently discontinued study drug due to a hyperglycemia TEAE. In the EU/NA Long-term Controlled Population, no patients reported a hyperglycemia TEAE leading to permanent discontinuation of study drug.

Reviewer's Comment: The data presented do not suggest that mirabegron 50 mg has the potential to cause glucose dysregulation.

Thyroid Function

Based upon FDA feedback regarding one report of an SAE of hypothyroidism (FDA End-of-Phase 2 meeting minutes, 14 November 2007) as well as a potential role of the beta receptor in thyroid function, a program-wide evaluation was conducted to assess the potential risk of thyroid dysregulation. The evaluation included results of thyroid function analytes collected in one of the phase 3 studies [Study 178-CL- 074] as well as a review of TEAE within the Thyroid Dysfunction SMQ (Broad).

In the EU/NA OAB 12-week Phase 3 Population, one or more thyroid function TEAE in the SOC of endocrine disorders was reported by 8/2736 (0.3 %) mirabegron, 5/1380 (0.4 %) placebo and 1/495 (0.2 %) tolterodine patients [ISS Table 6.9.1.2].

In the EU/NA Long-term Controlled Population, one or more thyroid function TEAE was reported by 10/1632 (0.6%) mirabegron patients (mirabegron 50 mg: 5/812 [0.6%]; mirabegron 100 mg: 5/820 [0.6%]) and 6/812 (0.7%) tolterodine patients.

Two thyroid function-related SAEs were reported in the mirabegron clinical program (one in the mirabegron 100 mg group [178-CL-044:111-1917-hypothyroidism] and one in the tolterodine group [178-CL-049:3113-2694-goitre]).

No patients in either the EU/NA OAB 12-week Phase 3 Population [ISS Table 6.9.3.2] or the EU/NA Long-term Controlled Population [ISS Table 6.9.3.3] experienced a thyroid function TEAE leading to permanent discontinuation of study drug.

Evaluation of mean, shift and PCS data for thyroid analytes collected during Study

178-CL-074 did not suggest differences across the total mirabegron, placebo and tolterodine treatment groups. Thyroid function TEAEs occurred in the Global OAB 12-week Phase 2/3 Population at a comparable frequency across treatment groups.

Reviewer's Comment: There is no suggestion from the data of thyroid dysregulation.

Urinalysis

The Sponsor concludes and I agree that the data from the clinical program do not suggest a clinically meaningful effect of mirabegron on urinalysis parameters.

Previous nonclinical studies indicated that mirabegron at high concentrations (0.25 mg/mL) could affect protein determinations by dipstick methodologies. Based on Study 178-TX-058, the Sponsor concludes that at the proposed dose of 50 mg, mirabegron is unlikely to effect protein determination in human urine.

Reviewer's Comment: Pharmacology/Toxicology, in their review, has calculated within the first six hours following 50 mg of mirabegron and in circumstances where the urine volume is between 125 and 250 ml, YM178 is unlikely to interfere with dipstick analysis. This potential is too remote to include in labeling.

7.4.3 Vital Signs

Pulse

In the EU/NA OAB 12-week Phase 3 Population, the adjusted mean difference vs placebo for change from baseline pulse rate in the EU/NA OAB 12-week Phase 3 Population receiving mirabegron 25, 50 and 100 mg and tolterodine was 0.9, 1.0, 1.9 and 1.0 bpm for AM measurements, respectively, and 0.6, 1.0, 2.3 and 2.1 bpm for PM measurements, respectively.

The adjusted mean change from baseline pulse rate in the EU/NA Long-term Controlled Population for the mirabegron 50 mg, 100 mg and tolterodine groups was 0.9, 1.6 and 1.5 bpm for AM measurements, respectively, and 0.4, 1.3 and 1.9 bpm for PM measurements, respectively.

Table 84: Pulse Rate Change Phase 3 Population

BPM (beats per minute)	Placebo	Mirabegron			Tolterodine
		25 mg	50 mg	100 mg	ER 4 mg
	(n=1380)	(n=342)	(n=1375)	(n=981)	(n=495)
AM					
Mean difference versus placebo (SE)		0.9 (0.40)	1.0 (0.24)	1.9 (0.28)	1.0 (0.36)
PM					
Mean difference versus placebo (SE)		0.60 (0.41)	1.0 (0.25)	2.3 (0.29)	2.1 (0.37)

Source: Table 1, Cardiovascular Research Report, Appendix 3, page 14

Table 85: Pulse Rate Change EU/NA Long-Term Population

BPM (beats perminute)	Mirabegron		Tolterodine
	50 mg	100 mg	ER 4 mg
	(n=812)	(n=820)	(n=812)
AM			
Adjusted mean change from baseline (SE)	0.9 (0.23)	1.6 (0.22)	1.5 (0.22)
PM			
Adjusted mean change from baseline (SE)	0.4 (0.24)	1.3 (0.37)	1.9 (0.24)

Source: Table 2, Cardiovascular Research Report, Appendix 3, page 16

Categorical increases from baseline in pulse rate in the EU/NA OAB 12-week Phase 3 Population were noted more frequently at various cut-points with mirabegron than with placebo. Mirabegron 25 and 50 mg were comparable to tolterodine while mirabegron 100 mg demonstrated more outliers at various cut-points than tolterodine.

In the EU/NA Long-term Controlled Population, the proposed therapeutic dose of 50 mg showed fewer outliers for increases from baseline at the various cut-points than either tolterodine or mirabegron 100 mg.

In the EU/NA Phase 3 OAB Population, TEAE related to rapid pulse rate (SOC Cardiac Disorders, preferred terms sinus tachycardia, supraventricular tachycardia, tachycardia and tachycardia paroxysmal: Table 5.5.1.3 ISS/SCS) occurred in 6/1380 (0.4%) placebo subjects, 5/432 (1.2%) mirabegron 25 mg subjects, 12/1375 (0.9%) mirabegron 50 mg subjects, 3/929 (0.3%) mirabegron 100 mg subjects and 2/495 (0.4%) tolterodine subjects. TEAEs related to rapid pulse rate (cardiac arrhythmia, mostly tachycardia) were more frequently observed in all active treatments (2.4% to 6.6%) than placebo (1.8%) in the Global OAB 12-week Phase 2/3 Population. The frequency of such events was comparable for all mirabegron doses of 100 mg or less (2.4% to 3.1%) and tolterodine (3.1%).

The Sponsor reports, in the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (3.9% and 4.1%, respectively) and was less than tolterodine (6.0%). Using the search terms (SOC Cardiac Disorders, preferred terms sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, tachycardia and tachycardia paroxysmal: Table 5.5.1.4 ISS/SCS), rapid pulse rate in the long-term study occurred 8/812 (1.0%) mirabegron 50 mg subjects, 5/820 (0.6 %) mirabegron 100 mg subjects and 12/812 (1.5%) tolterodine subjects.

Female patients demonstrated a generally higher increase in pulse rate compared with male patients, although this finding was inconsistent across treatment groups and AM/PM measurements. In patients who received the proposed mirabegron therapeutic dose of 50 mg, pulse rate changes from baseline compared with placebo were approximately 1 bpm or less and pulse rate changes from baseline were similar to those in patients who received tolterodine, in both the 12-week studies and the long-term study, in both genders.

Overall data 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 change from baseline to final visit in pulse rate for patients < 65 years vs \geq 65 years in any treatment group, while in the long-term study, changes from baseline AM and PM pulse rate were greater in patients < 65 years of age than in patients \geq 65 years of age. Pulse rate changes in the mirabegron 50 mg and 100 mg groups were similar or less than the changes in the tolterodine group in both age groups. In an additional analysis categorizing patients into < 45 years, 45 to < 65 years and \geq 65 years of age, for PM measurements, change from baseline and difference vs placebo in change from baseline were generally smaller in older compared with younger patients receiving mirabegron or tolterodine, with the greatest change generally seen in patients < 45 years of age in the 12-week studies. This pattern was not discernible in the AM measurements.

In the long-term study, similar results were observed in the adjusted mean change from baseline for pulse rate. Patients who received mirabegron 50 mg, the proposed therapeutic dose, had a difference vs placebo in change from baseline pulse rate of approximately 1 bpm or less in all 3 age categories, except for a 3 bpm increase in PM but not AM pulse rate in patients < 45 years of age in the 12-week studies. Pulse rate changes in patients who received mirabegron 50 mg were similar to those in patients who received tolterodine, in both the 12-week studies and the long-

term study in all 3 age categories. This included greater increases in the placebo-difference change from baseline in PM but not AM pulse rate for patients < 45 years of age in the 12-week studies.

The overall frequency of atrial fibrillation TEAE in the EU/NA Phase 3 OAB Population was low (0.1 %, 0.0 %, 0.3 %, 0.4 %, 0.2 % and 0.6% for placebo, mirabegron 25, 50, 100 and 200 mg, and tolterodine, respectively: Table 5.3.3 ISS/ICS) and comparable for mirabegron and tolterodine in the Global OAB 12-week Phase 2/3 Population.

In Study 077, which was a thorough QT study in healthy volunteers, the mean pulse rate at hour 3 on the final day was increased 4.3 bpm (SE 0.82) over placebo for mirabegron 50 mg subjects. In Study 031, which included elderly subjects, the mean pulse rate on hour 4 of the final day increased over placebo by 2.8 (SE 1.7) bpm. In both these studies, dosing was done fasting and subjects were inpatients.

Reviewer's Comment: In Phase 3, the mirabegron-related increase in pulse rate was less than observed in Phase 1 studies 077 and 031. Phase 3 determinations may not have measured pulse rates at peak exposure.

Overall, the increase in pulse rate in the OAB phase 3 population associated with the proposed therapeutic dose of mirabegron 50 mg was approximately 1 bpm, similar to tolterodine and did not result in more outliers or tachycardia-related AE than observed with tolterodine. The placebo-subtracted increases in pulse rate for mirabegron 50 mg observed in Phase 1 studies 077 and 031 was between 2.8 bpm and 4.3 bpm.

Reviewer's Comment: In Phase 3 studies, the to-be-marketed dose of 50 mg appears to be associated with a pulse increase of 1 bpm. The mirabegron-related increase in pulse rate was higher in Phase 1 studies, The increase in pulse rate secondary to mirabegron appears to be modestly greater in women compared to men, and in younger compared to older patients. The mirabegron-related increase in pulse is not of itself a safety concern.

Blood Pressure

In Phase 3 studies, mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with an approximately 1 mm Hg adjusted mean difference for change from baseline in SBP/DBP compared with placebo. The adjusted mean difference vs placebo for change from baseline SBP in the EU/NA OAB 12-week Phase 3 Population for mirabegron 25, 50 and 100 mg and tolterodine was -0.6, 0.7, 0.2 and -0.4 mm Hg for AM measurements, respectively, and -1.0, 0.5, 0.9 and 0.0 mm Hg for PM measurements, respectively.

The adjusted mean difference vs placebo for change from baseline DBP in the EU/NA OAB 12-week Phase 3 Population in mirabegron 25, 50 and 100 mg and tolterodine was -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements, respectively, and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.

Table 86: Systolic Blood Pressure Phase 3 Population

Systolic Blood pressure	Placebo	Mirabegron			Tolterodine
	(n=1380)	25 mg (n=342)	50 mg (n=1375)	100 mg (n=981)	ER 4 mg (n=495)
AM Week 12					
Mean difference versus placebo (SE)		-0.6 (0.56)	0.7 (0.36)	0.2 (0.41)	-0.4 (0.52)
PM					
Mean difference versus placebo (SE)		-1.3 (0.57)	0.5 (0.37)	0.8 (0.42)	-0.2 (0.53)

Source: Table 9.3.1.1 Cardiovascular Research Report, Appendix 4

In the EU/NA Long-term Controlled Population, the adjusted mean changes from baseline SBP and DBP following mirabegron 50 mg, mirabegron 100 mg and tolterodine were generally similar. The adjusted mean change from baseline for SBP in mirabegron 50 and 100 mg and tolterodine was 0.2, 0.4 and -0.5 mm Hg for AM measurements, respectively, and -0.3, 0.1 and 0.0 mm Hg for PM measurements, respectively. The adjusted mean change from baseline for DBP in mirabegron 50 and 100 mg and tolterodine was -0.3, 0.4 and 0.1 mm Hg for AM measurements, respectively, and 0.0, 0.1 and 0.6 mm Hg for PM measurements, respectively.

Table 87: Systolic Blood Pressure Long Term Population Change to Endpoint by Patient Diary

Systolic Blood pressure	Mirabegron		Tolterodine
	50 mg (n=812)	100 mg (n=820)	ER 4 mg (n=812)
AM			
Adjusted mean change from baseline (SE)	0.2 (0.33)	0.4 (0.33)	-0.5 (0.33)
PM			
Adjusted mean change from baseline (SE)	-0.3 (0.33)	0.1 (0.33)	-0.0 (0.33)

Source: Table 49, 178-CL-049 Study Report, page 191

The Sponsor states that TEAE related to hypertension were similar for the total mirabegron (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]) groups in the EU/NA OAB 12-week Phase 3 Population. The frequency of such events was comparable for mirabegron 50 mg (120/1375 [8.7%]) or 100 mg (58/929 [6.2%]) and was highest in mirabegron 25 mg (52/432 [12.0%]). In the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (89/812 [11.0%]) and 83/820 [10.1%]) and tolterodine (86/812 [10.6%]).

Male patients had generally larger changes from baseline compared to females in adjusted mean difference vs placebo in the 12-week studies and adjusted mean changes in the long-term study in SBP/DBP, although this finding was inconsistent across treatment groups and AM/PM measurements.

Overall data suggested a greater effect of mirabegron on SBP/DBP in younger compared with older patients, although this finding was inconsistent. No consistent trend of SBP/DBP change was evident in patients < 65 years of age compared with patients \geq 65 years of age. In the 12-week studies, changes in adjusted mean differences vs placebo were generally similar in both age groups. In the long-term study, adjusted mean changes in AM/PM SBP were larger in patients \geq 65 years, while changes in AM/PM DBP were larger in patients < 65 years of age. This trend in the long-term study was seen in both the mirabegron and tolterodine treatment groups. In an additional analysis categorizing patients into < 45 years, \geq 45 to < 65 years and \geq 65 years of age, baseline SBP was higher in older patients, across the age categories and in all treatment groups in both the 12-week studies and in the long-term study. Baseline DBP was generally similar across age categories. In the 12-week studies, adjusted mean difference vs placebo in change from baseline SBP/DBP was generally smaller in older compared with younger patients who received mirabegron, with the greatest change generally seen in patients < 45 years of age. However, the SBP analysis is potentially confounded by age differences in the changes from baseline on placebo; the adjusted changes from baseline SBP, when not corrected for placebo, are generally larger in the patients >65 years of age than in those <45 years of age. This trend was also seen in the adjusted mean change from baseline DBP measurements in the long-term study while the adjusted mean change from baseline in SBP was generally higher for patients \geq 65 years of age. Patients who received mirabegron 50 mg, the proposed therapeutic dose, had an adjusted mean difference vs placebo and an adjusted mean change from baseline SBP/DBP of approximately 1 mm Hg or less in the 12-week studies and the long-term study, respectively, comparable to tolterodine in both younger and older patients. Mirabegron-related increase in blood pressure were larger in Phase 1 studies compared to Phase 3 studies.

Reviewer's Comment: The findings of increases in pulse and blood pressure in Phase 1 and 3 studies were presented to an FDA Advisory Committee which considered them in their deliberations.

In looking at Phase 1 Study 077, a through QT study in healthy volunteers, at hour 3 on the final study day, mean systolic blood pressure in mirabegron 50 mg subjects was increased as compared to placebo by 4.0 mmHg (SE 1.01). In the Phase 1 Study 031, which was a pharmacokinetic and tolerability study in young and elderly subjects, at hour 4 on the final study

day, the increase in mean systolic blood pressure as compared to placebo was 5.5 mmHg. This was the time of maximal effect. Dosing in these studies was fasting and patients were admitted to a testing facility.

In Phase 3 studies, objective *decreases* in blood pressure and/or hypotension were similar across treatment Groups.

Due to its potential relevance to increased blood pressure, the incidences of AEs of cardiac failure were analyzed. In the Global OAB 12-week Phase 2/3 Population, the TEAE of congestive heart failure (CHF) based on the SMQ of cardiac failure occurred in 14/2142 (0.7%), 4/811 (0.5%), 14/2131 (0.7%), 15/1305 (1.1%), and 5/958 (0.5%) patients in 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 edema not elsewhere classified (NEC) (29/33 patients in the total mirabegron group). In the Phase 3 pivotal studies the incidences of heart failure using the higher level term were: 0/1330 for placebo, 0/432 for mirabegron 25 mg, 0/1375 for mirabegron 50 mg, 3/929 (0.3%) for mirabegron 100 mg and 0/495 for tolterodine. In the EU/NA Long-term Controlled Population, TEAE of CHF based on the SMQ of cardiac failure occurred in 10/812 (1.2%), 6/820 (0.7%) and 9/812 (1.1%) patients 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).

To assist in DRUP's analysis of the effect of mirabegron upon blood pressure, a consultation from the Cardiovascular and Renal Products (DRCP) was obtained. The consultant's findings are summarized herein:

- The consultant found that the Sponsor's assessment of the effect of mirabegron in Phase 3 studies was accurate.
- It could not be concluded that pre-existing hypertension (Hypertension Status 1 definition) increased the risk of medically important elevations of the SBP or DBP in patients treated with mirabegron relative to the normotensive population.
- Categorical changes from baseline show numerically higher percentages of patients at the final visit SBP and DBP elevations on 50mg mirabegron than for tolterodine, a commonly used anticholinergic used to treat overactive bladder (OAB), but the same is true for placebo (numerically higher percentages of patients at the final visit SBP and DBP elevations). The consultant theorizes this may be an artifact of the program design, in that all of the Phase 3 tolterodine data in the Sponsor's table was generated from European trial 046, while the placebo and mirabegron data columns are an integration of data from trials 046 and 047, the latter of which includes data from the US. Thus, comparing 50mg mirabegron only to placebo, the differences in final visit categorical SBP/DBP elevation rates are less < 2%. Consecutive visit category elevations demonstrate that the numerical differences in rates between placebo and mirabegron are mostly driven by lower degrees of SBP/DPB elevations, and that some of the PM tolterodine elevation rates are higher than for 50mg mirabegron.
- There are no trends for change from baseline in DBP or SBP with increasing exposure to mirabegron.

- Potentially clinically significant blood pressure findings were assessed for both the 12-week phase III and the long-term controlled EU/NA populations. The occurrence of these events was comparable between all of the treatment groups

Reviewer's Comment: In Study 074, categorical increases in systolic BP ≥ 5 mmHg, ≥ 10 mmHg, and ≥ 15 mmHg were greater for mirabegron compared to placebo

- Increasing risks for cardiovascular events with increasing levels of blood pressure are a continuum (i.e., these risk curves [generated from longitudinal studies] do not demonstrate risk thresholds as a function blood pressure, but increase continuously), and the increase in relative risk per mmHg of BP increase is the same regardless of baseline BP. Consequently, the absolute risk of increasing SBP from 169 to 170 is worse than increasing SBP from 119 to 120. Superimposed on this phenomenon are the effects of other risk modifiers, such as smoking status and diabetes. Therefore small incremental in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) should not be discounted with out further analysis.
- In order to provide DRUP with some estimate of the clinical significance of the mirabegron-associated small increases in BP, DCRP put the target population's blood pressure data and demographic characteristics into a Framingham risk model to predict the possible impact on major cardiovascular (CV) event rates for the observed blood pressure effects. Actual data for each subject's true blood pressure shifts were used. Data that was unknown (e.g. serum lipid levels) were imputed from known databases.

At the Advisory Committee meeting, where the safety and efficacy of mirabegron was discussed, DRCP presented their exploratory analysis of the mirabegron BP data using the Framingham risk model. Using the small mirabegron-associated BP elevations observed in Phase 3, in a high risk group (OAB patients with cardiac risk factors such as hypertension, obesity, tobacco use, hyperlipemia and diabetes), the mirabegron-related BP increase translated into an estimated 556 more cardiovascular events per million patients per year with mirabegron compared to with placebo. In the broad population (not high risk), 187 more cardiovascular events per million patients per year were predicted for mirabegron compared to placebo. Using the mirabegron-associated SBP increase in the Phase 1 TQT study (3 mmHg), and considering all subjects (not just high risk), the predicted incidence of cardiovascular events was 956 events for mirabegron versus 117 events for placebo per million patients per year.

The Advisory Committee considered these exploratory observations, along with the results from ambulatory blood pressure monitoring in 20 patients in Study 049, which did not show any mirabegron-related increase in the blood pressure compared to tolterodine.

Reviewer's Comment: Hypertension as a reported clinical AE was modestly increased in incidence with mirabegron compared to with placebo. On further scrutiny, none of these cases were new onset hypertension, but in some cases, there was an exacerbation of pre-existing hypertension. In phase 3 pivotal studies, there is agreement that mirabegron increases the blood pressure 0.5-1.0 mmHg. The blood pressure increases may be larger, as noted in Phase 1 Studies

031 and 077, but the Phase 1 studies may not represent the clinical population or clinical situation. Ambulatory blood pressure monitoring in a small number of patients in the 1 year long-term study did not reveal increases in blood pressure compared to an active control. Mirabegron also increases the pulse rate modestly.

The reviewer agrees with the majority of the AC that the current information concerning mirabegron's effect on the blood pressure and pulse does not preclude approval. However, the reviewer also agrees with the AC that the label should disclose these potential risks, and that patients with uncontrolled hypertension should probably avoid use of mirabegron. In addition, the reviewer agrees with the AC that additional investigation of this issue ("monitoring") would be appropriate in the postmarketing period. A long term postmarketing study should be requested to further assess public health consequences of mirabegron therapy with regard to cardiovascular events. This trial may need to be years in length and should be devised with input from Epidemiology.

7.4.4 Electrocardiograms (ECGs)

The Sponsor states there are no trends observed in the ECG intervals across treatments and subgroups in either the EU/NA OAB 12-week Phase 3 Population or the EU/NA Long-term Controlled Population. The Sponsor also states there are also no consistent trends for ECG abnormalities, except for mirabegron-related increases in heart rate, and selected arrhythmia, mostly sinus tachycardia.

In regard to the effect of mirabegron on the QT interval, in the Sponsor's initial QT Study (178-CL-037), post-hoc analyses showed that the original analysis did not adequately correct for mirabegron-induced increases in heart rate. When the Sponsor reanalyzed the results using multiple corrections for pulse rate, it appeared that mirabegron in females at 200 mg had a mean treatment difference on the corrected QT interval of 15.0 msec when compared to placebo (upper bound of 95% CI =18.0 msec). To resolve this issue, the Sponsor initiated a repeat TQT study (178-CL-077) which included 352 subjects. In this large TQT study, in the overall population (both female and male volunteers), at the therapeutic dose of mirabegron (50 mg), the mean treatment difference compared to placebo was below 5 msec and the upper bound of the 1-sided 95% CI for the QTcI interval was less than 10 msec at all evaluated time points. At the suprathreshold dose of mirabegron 100 mg, the mean treatment difference was above 5 msec only at the 3.0 to 4.5 hour time points and the upper bound of the 1-sided 95% CI for the QTcI interval was less than 10 msec at all evaluated time points. At a higher suprathreshold dose (mirabegron 200 mg) the point estimate was above 5 msec at all evaluated time points but the upper bound of the 1-sided 95% CI did not exceed 10 msec at any evaluated time points.

Therefore, in Study 077, by regulatory standard, mirabegron did not produce QT prolongation at any dose. At the suprathreshold dose of 100 mg, C_{max} and AUC_{tau} were approximately 2.9- and 2.6-fold higher than at the therapeutic dose of 50 mg. At the 200 mg dose, which increased

C_{max} and AUC by approximately 8.4- and 6.5-fold, respectively compared to the therapeutic dose, the mean increase in QT_c was > 5 msec at all timepoints, but the upper bound of the 95% CI did not exceed 10 msec at any timepoint – thus meeting the current regulatory standard for not prolonging the QT interval.

However, in Study 077, in a subgroup analysis by gender, at the 200 mg mirabegron dose, the maximum increase of QT_{c1} in female volunteers was 10.42 msec. The 90% CI (at 5 hours) was 7.40, 13.44 msec. Thus, the 90% CI is modestly above 10 msec, the strict regulatory limit for lack of QT prolongation. In this study, in male volunteers, at no time did the 90% CI exceed 10 msec in the mirabegron 50 mg, 100 mg and 200 mg dose groups in males. At mirabegron doses of 50 mg and 100 mg, at no timepoint did the 90% CI go above 10 msec in female subjects. Of note, female volunteers had approximately 30% to 60% higher mean C_{max} and 40% to 50% higher mean AUC_{tau} of mirabegron than male volunteers, but a large percentage of this difference is due to differences in body weight.

A consultation was requested from the Interdisciplinary Review Team-QT (IRT-QT) and a completed report was forwarded to the Division on 24 January 2012. The conclusion of the IRT-QT was “*No significant QT_c prolongation effect of mirabegron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta \Delta$ QT_{c1} for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated indicating that assay sensitivity was established.*”

Study 077 was a randomized, blinded, four-treatment-arm, parallel-crossover design study. A total of 352 healthy subjects received either mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, mirabegron 200 mg and placebo, or a single oral dose of moxifloxacin 400 mg and placebo. 25 mg and 50 mg are the therapeutic doses. 25 mg is also to be used in patients with severe renal impairment or moderate hepatic impairment. The supratherapeutic doses of 100 mg and 200 mg produced C_{max} that was 2.9-fold and 8.4-fold, and AUC that was 2.6-fold and 6.5-fold, respectively, those with 50 mg. The exposures achieved with 200-mg dose were even higher, and were adequate to cover any clinical exposure scenario. A positive exposure-response relationship was observed for mirabegron; however, there was no substantial QT_c prolongation expected observed with therapeutic dose of 50 mg, and by strict regulatory standard (90% CI comparing treatment group to placebo for change from baseline exceeding 10 msc), there was no QT_c prolongation at any dose. Females having 40 to 50% higher exposures compared to males that may explain the larger effect of mirabegron on QT_c for females, but there was no effect of gender on the concentration-QT slope.

In this TQT study, mirabegron increased heart rate on ECG in a dose-dependent manner. The maximum mean difference from placebo after adjusting for baseline (with 90% confidence interval) was 6.7 bpm (5.3, 8.1), 11 bpm (9.4, 12.6) and 17 bpm (15.3, 18.7) for 50 mg, 100 mg and 200 mg, respectively. For female subjects only, the maximum mean difference from placebo (90% confidence interval) was 8.3 bpm (6.0, 10.7), 13.6 bpm (11.2, 16.0) and 20.0 bpm (17.6,

22.3) bpm for 50 mg, 100 mg and 200 mg, respectively. The maximum increases in HR on ECG occurred between 5 and 6 hours post-dose which is consistent with the Tmax of mirabegron.

In answers to the Division's questions, the IRT-QT stated:

- The study design used was acceptable.
- The methodology used in Study 178-CL-077 was appropriate to correct for increases in heart rate.
- The IRT-QT team agreed with the Sponsor's assessment of the results from Study 178-CL-077.
- The IRT-QT team agreed that the TQT studies supported the safety of mirabegron at doses of 25 and 50 mg with respect to mirabegron's effect on the QT interval.
- The IRT-QT team has no additional recommendation regarding the QT interval but did have label recommendations for the Division to consider. The IRT-QT stated that a Warning and Precaution section was not needed. The IRT-QT team recommended consideration of the following label language. The recommendation was proposed as a suggestion only:

“12.2 PHARMACODYNAMICS

Cardiac Electrophysiology

The effect of multiple doses of mirabegron 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. Dose and exposure related prolongation in QT interval was observed with mirabegron. However, no substantial QT prolongation is expected with clinically relevant exposures. The dose of 200 mg once daily mirabegron is adequate to represent the high exposure clinical scenario. In this thorough QT study, mirabegron increased heart rate on ECG in a dose dependent manner. The maximum mean difference from placebo after adjusting for baseline (90% confidence interval) is 6.7 (5.3, 8.1), 11 (9.4, 12.6) and 17 (15.3, 18.7) bpm for 50 mg, 100 mg and 200 mg, respectively. For female subjects only, the maximum mean difference (90% confidence interval) is 8.3 (6.0, 10.7), 13.6 (11.2, 16.0) and 20.0 (17.6, 22.3) bpm for 50 mg, 100 mg and 200 mg, respectively.”

Reviewer's Comment: The QT prolongation review issue is considered resolved. The increase in heart rate in this study is notable.

The following are key findings from the Sponsor's summary of the overall ECG data from the NDA:

- In the Phase 3 studies, all mirabegron treatment groups had a decrease in mean QTcF from baseline to 12 weeks of approximately 2 msec; the decrease observed for mirabegron 200 mg was slightly larger at 4.4 msec.
- There was a higher occurrence of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo. QTc measurements exceeding these thresholds occurred with similar frequency in patients receiving mirabegron 25, 50 and 100 mg and placebo.
- Maximum QTcF values > 450 msec occurred more often in female than male patients with a comparable frequency in all treatment groups except for mirabegron 200 mg. No differences were observed between male and female patients in the frequency of maximum change from baseline in QTcF of ≥ 30 msec.
- Elderly OAB patients (≥ 65 years of age) had a higher frequency of maximum QTcF values > 450 msec which did not differ by treatment groups in the 12 week Phase 3 population. The frequency of maximum changes from baseline > 30 msec were similar for patients < 65 years and ≥ 65 years of age. QTcF values > 500 msec were observed in 1 patient < 65 years of age (tolterodine: 1/266 [0.4%]) and in 2 patients ≥ 65 years of age (placebo: 1/479 [0.2%] and mirabegron 100 mg: 1/325 [0.3%]). Across the dose groups, the frequency of change from baseline in QTcF ≥ 30 msec and < 60 msec was generally higher in patients ≥ 65 years of age; within age groups the frequency of changes ≥ 30 msec was generally similar across the treatment groups. Change from baseline in QTcF ≥ 60 msec was reported in 5 patients < 65 years of age (placebo: 1/765 [0.1%]; mirabegron 25 mg: 0; mirabegron 50 mg: 1/757 [0.1%]; mirabegron 100 mg: 2/507 [0.4%]; tolterodine: 1/256 [0.4%]) compared with 3 patients ≥ 65 years of age (placebo: 1/467 [0.2%]; mirabegron 25 mg: 1/147 [0.7%]; mirabegron 50 mg: 0; mirabegron 100 mg: 0; tolterodine: 1/165 [0.6%]).
- There were very few SAE, TEAE and CV adjudicated events that involved QT prolongation or ventricular arrhythmias and there was no difference between the frequency of these events in the mirabegron, placebo, and tolterodine groups. No events of torsades de pointes were reported in any patient in the mirabegron clinical program.

Reviewer's Comment: Mirabegron 200 mg was associated with a modest increase above the regulatory standard for QT interval prolongation in females (upper bound of 90% CI of 13.4 msec). It may be appropriate to mention this in the Electrophysiology section of labeling. At the planned to be marketed doses, the incidence of clinically significant prolongation of the QT interval ≥ 450 msec occurred in similar frequency as compared to placebo patients.

The increased incidence of QTcF increases in females compared to males does not raise a concern because there is no difference between placebo and either mirabegron 50 mg or mirabegron 100 mg in either gender. There are no significant differences related to age and any mirabegron-associated effect on QT.

The Sponsor concludes:

- At the proposed therapeutic dose, mirabegron 50 mg did not have a clinically meaningful treatment effect on QTc interval in females or males.
- A modest increase above the regulatory standard (13.4 msec versus 10 msec for the upper bound of the 90% CI) was observed in females at a suprathreshold mirabegron dose of 200 mg and this treatment effect might be attributable to higher mirabegron exposure in females. A 200 mg dose of mirabegron is associated with an 8.4- and 6.5-fold increased C_{max} and AUC_{tau} compared with the proposed therapeutic dose of mirabegron 50 mg, and an even greater margin for the starting dose of mirabegron 25 mg.
- In OAB patients, there was a higher frequency of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo and compared with the lower mirabegron dose groups. Female patients had higher frequency of maximum QTcF values > 450 msec than male patients; but there was no difference between mirabegron and placebo by gender for the relevant mirabegron doses of 50 mg and 200 mg.

Reviewer's Comment: There appears to be no significant risk for QT prolongation when mirabegron is used as labeled.

7.4.5 Special Safety Studies/Clinical Trials

The potential for urinary retention and bladder function decompensation in men with lower urinary tract symptoms (LUTS) and known bladder outlet obstruction (BOO) was assessed by post-void residual urine (PVR) and urodynamic parameters in Study 178-CL-060. Urodynamic safety results demonstrated that treatment with mirabegron 50 mg and 100 mg once daily did not result in a decrease in maximum urinary flow rate (Q_{max}) nor in an increase in detrusor (voiding) pressure at maximum flow rate (P_{det}Q_{max}) in patients with LUTS and BOO compared with treatment with placebo. A dose-dependent increase in PVR volume was observed at week 12 and end of treatment in mirabegron-treated patients which achieved statistical significance (P = 0.0459) at the end of treatment in the mirabegron 100 mg group. These changes were approximately 30 mL relative to the placebo group and are not considered to be clinically meaningful. Two TEAE of urinary retention occurred, one in the placebo group, which required catheterization, and one in the mirabegron 100 mg treatment group, which resolved without invasive intervention (abdominal palpation). Both episodes of urinary retention lasted approximately 1 day in duration.

Reviewer's Comment: In this study, mirabegron in male OAB patients with LUTS/BOO (Lower Urinary Tract Symptoms/Bladder Outlet Obstruction) did not increase the risk of urinary retention or worsening of bladder function.

7.4.6 Immunogenicity

During the mirabegron clinical development program, 2 events with findings suggestive of drug hypersensitivity reaction reported in 2 subjects (investigator-reported as preferred terms [PTs] of Stevens-Johnson syndrome [SJS] in [Patient No. 178-CL-045, P00244] and leukocytoclastic

vasculitis in [Volunteer No. 178-CL-076, U00022981217]) prompted a program-wide evaluation of potential hypersensitivity events and resulted in the Hypersensitivity Research Report as part of the NDA submission. A broad and sensitive, but nonspecific, search strategy using prespecified Standardized MedDRA Queries (SMQs) was employed to capture potential hypersensitivity events [Module 5.3.5.3 ISS, Appendix 2 (ISS SAP, Appendix 8)]. An independent Expert Committee (2 dermatologists and one allergist/immunologist) reviewed individual cases that were generated by the database search. The committee was provided with subject data packages, blinded to study treatment assignment, for subjects with potential hypersensitivity events, to identify plausible and definite hypersensitivity reactions and assess causal relationships with study drug.

Of 9832 total subjects across all treatment groups, the Expert Committee reviewed subject data packages for 257 subjects (2.6%) with 290 potential hypersensitivity events and identified 44 subjects (0.4%) with 50 plausible hypersensitivity reactions. Of the 44 subjects with plausible hypersensitivity reactions: 31 patients were from Global 12-week Phase 2/3 Population, 12 patients were from EU/NA Long-term Controlled Population and 2 volunteers were from Global Phase 1 Population [Tables 4.1, 4.2, 4.3 and 4.4]. One patient had plausible hypersensitivity reactions in a Global 12-week Phase 2/3 Study (178-CL-046) and in the EU/NA Long-term Study and was counted in each population. The reactions in these 44 subjects were categorized as: 2/9832 (< 0.1%) immediate-type; 33/9832 (0.3%) nonimmediate-type, primarily cutaneous; 6/9832 (0.1%) nonimmediate-type, primarily noncutaneous; and 5/9832 (0.1%) hypersensitivity of undetermined type.

Table 88: Plausible Hypersensitivity Reactions to Mirabegron

Hypersensitivity Reactions	Placebo	Mirabegron					Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	200 mg	300 mg	
All	2	3	8	21	2	2	6
Possibly Related	1	1	5	17	2	2	5
Phase 3	2 (n=1380)	1 (n=432)	3 (1375)	8 (n=495)	0	0	4 (n=495)
Phase 3 Possibly Related	1	1	3	7	0	0	3
Long Term	0	0	2 (n=812)	7 (n=820)	0	0	1 (n=812)
Long Term Possibly Related	0	0	1	6	0	0	1

“Possibly related” to mirabegron as determined by the adjudication committee.

Source: Table 4 Hypersensitivity Research Report, page 43

Within the immediate type hypersensitivity reactions there was one placebo subject who had urticaria and one mirabegron 100 mg phase 3 subjects who developed generalized pruritis. No patient developed anaphylaxis or angioneurotic edema.

Nonimmediate primarily cutaneous reactions were reported in 29 subjects (8 in the long term study and 10 in the Phase 3 studies). Urticaria was reported in 14 patients, rash in 7 patients, pruritis in 4 patients, and purpura in one patient. Rash was reported in three tolterodine patients. Leukocytoclastic vasculitis was reported in two patients (178-CL-047: patient U00018156541 [mirabegron 50 mg: onset Day 21] and 178-CL-076: patient U00022981217 [mirabegron 100 mg: onset Day 31 after 4 single doses mirabegron 100 mg each separated by a 10 day washout period]).

Reviewer's Comment: The role of mirabegron in the two leukocytoclastic vasculitis cases is unclear but mirabegron cannot be excluded as a potential cause.

Non-immediate primarily noncutaneous hypersensitivity reactions were reported in 4 patients: one patient in the phase 3 studies (178-CL-046: mirabegron 100 mg: edema), 1 in the EU/NA long term study (Patient 2037-0516: mirabegron 100 mg: hemolytic anemia and thrombocytopenia), and one patient each in Study 178-CL-044 (neutropenia) and in Study 178-CL-045 (leukopenia). Stomatitis was reported in two tolterodine patients in Study 178-CL-046.

Reviewer's Comment: The leukopenia case in Study 178-CL-045 was analyzed in great detail. Patient P00244, randomized to mirabegron 100 mg, was reported as having leukopenia on Day 28. She also had developed urticaria on her legs, and elevations of liver function tests. By Day 35, the patient had generalized urticaria extending over her entire body, fever of 38.5°C, and generalized malaise. The diagnosis at that time was Stevens-Johnson Syndrome (SJS). It is of note that the patient had had a recent viral infection and had used an over the counter remedy, Kyufu Gold. A drug lymphocyte stimulation test (DLST) was performed on 26 May 2008, approximately four and a half months after onset of increase in liver chemistries and rash. The study employed the use of Kyufu Gold, mirabegron placebo, and mirabegron tablet as test antigens. Of note, the Kyufu Gold used for DLST testing was a new sample and not taken from the expired sample that the subject had originally consumed on day 24. Drug lymphocyte stimulation results compared with control were 99% (1654 counts per minute [cpm]) for Kyufu Gold, 117% (1956 cpm) for mirabegron placebo and 194% (3226 cpm) for mirabegron (MedWatch report, 2010-10-14). This patient did not have mucous membrane lesions, nor blisters, nor skin erosions with positive Nikolsky's sign, thus it is not clear that the patient actually had SJS. The DLST results imply a role of mirabegron in the event, although the role of Kyufu Gold remains unclear.

Mirabegron is already approved for marketing in Japan. Spontaneously reported post marketing adverse events in Japan have been submitted to IND 69,416. One of these adverse events is relevant to a discussion of hypersensitivity reactions. The Agency had received Manufacturer's Report Number 2011JP008642. In the initial report (12 December 2011), the event was described as erythema multiforme. The subject is 86 years old Japanese female. On October 14, 2001, the patient began mirabegron 50 mg for OAB. Prior to initiation of mirabegron therapy, "the patient had rash, which was so mild as to pose little problem." On 15 November 2011, the rash spread to all over the body and by November 19, 2011, the entire body was involved with

the exception of the face. There were no symptoms such as fever, arthralgia, swollen lymph nodes, angioedema, decrease of blood pressure, blisters/bullous lesions, mucosal erosion or skin exfoliation. There are no laboratory tests included in the report. There is no photograph of the skin lesions. The patient had no prior history of drug allergies or other allergic conditions. There were no concomitant medical products or other relevant medical history included in the report. The patient was not hospitalized and responded to topical and oral steroid based therapy.

Reviewer's Comment: It is not clear that the patient had erythema multiforme.

Reviewer's Overall Comment: The incidence of plausible and possibly related hypersensitivity reaction adverse event reports was higher in mirabegron subjects than it was in placebo subjects. There was one immediate hypersensitivity reaction in a 100 mg mirabegron patient (pruritis) and one case in a placebo patient. There were no cases of anaphylaxis or angioedema. In the non-immediate hypersensitivity category, there were 29 reports in mirabegron-treated patients (7 in mirabegron 50 mg subjects and 3 in mirabegron 25 mg subjects), one in a placebo subject, and three in tolterodine subjects. Leukocytoclastic vasculitis was reported in two patients (mirabegron 100 mg and mirabegron 50 mg). In terms of non-immediate primarily noncutaneous hypersensitivity reactions, hemolytic anemia/thrombocytopenia was reported in one patient (mirabegron 100 mg). There were also two 100 mg subjects who had an undetermined type of hypersensitivity reaction. An additional mirabegron 100 mg patient in Study 178-CL-049 (#1630-6655) had liver biopsy changes compatible with drug induced hepatic injury (DILI) or autoimmune hepatitis.

Overall then, as described in the cases above, there have been a small number of reports of clinically significant hypersensitivity reactions in patients taking mirabegron. An association between mirabegron and these events is possible. In several cases, hypersensitivity and hepatotoxicity were observed in the same patient, and a role of mirabegron in these specific events can not be ruled out.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the 12-Week, Phase 3 population the overall incidence of adverse events was:

Table 89: TEAE by Dose Group Phase 3 Population

MedDRA v12.1 (n%) of Patients	Placebo (n=1380)	Mirabegron			Tolterodine ER 4 mg (n=495)
		25 mg (n=432)	50 mg (n=1375)	100 mg (n=929)	
Overall	658 (47.7%)	210 (48.6%)	647 (47.1)	402 (43.3)	231 (46.7)
TEAE by PT Reported by $\geq 3.0\%$ in Total Mirabegron Group					
Hypertension	105 (7.6)	49 (11.3)	105 (7.5)	45 (5.2)	40 (8.1)
Nasopharyngitis	3 (2.5)	15 (3.5)	54 (3.9)	25 (2.7)	14 (2.8)
UTI	25 (1.8)	18 (4.2)	40 (2.9)	25 (2.7)	10 (2.0)
Overall SAEs Non-fatal	29(2.1)	7(1.6%)	29(2.1)	26(2.8%)	11(2.2)
TEAE Leading to Discontinuation	46 (3.3)	17 (3.9)	53 (3.9)	34 (3.7)	22 (4.4)

Source: Table 23, SCS, page 57, Review Table 68, Table 48, ISS page 144,

The true incidence of hypertension is lower than that shown in the preceding table. There were few, if any, cases of new-onset hypertension and most hypertension AE cases consisted of variability around known baseline elevated BP. There was no dose-relatedness for serious cardiovascular events. There were no reports of myocardial infarction in the 12-Week, Phase 3 studies. Among a small number of reports, a dose response was observed for palpitations and for supraventricular arrhythmia, primarily the benign supraventricular arrhythmia of sinus tachycardia. With respect to non-serious hypersensitivity reactions, there is a dose-dependent association (see Table 84). With respect to hepatic investigations, there was no evidence of dose dependency – there is just one finding amongst a plethora of analyses that may show something of an association between mirabegron and increase in liver function tests: changes from baseline to endpoint in serum ALT were 0.3, 1.2, 0.5, and 1.3 U/L, for placebo, mirabegron 25 mg, 50 mg and 100 mg respectively. The changes from baseline to endpoint in AST were for placebo, mirabegron 25 mg, 50 mg and 100 mg, 0.3, 1.0, 0.3, and 1.8 U/L respectively. With respect to pulse rate and blood pressure, there appears to be dose dependent relationship in Phase 1 studies only. This relationship is most notable at doses greater than 50 mg.

Reviewer's Comment: The frequency of various TEAEs is higher at 25 mg compared to 100 mg. Few AEs demonstrate dose relatedness. There does appear to be a modest dose-dependency for SAEs and AEs leading to discontinuation. The safety results when analyzed by gender (see Table 87) do not support an overall increase in SAEs or AEs based on dose. I cannot conclude there is an increase in adverse events overall based on dose for mirabegron.

7.5.2 Time Dependency for Adverse Events

Table 90: Overall Adverse Events Phase 3 versus Long-term Use Populations

MedDRA v12.1 (n%) of Patients	Placebo (n=1380)	Mirabegron			Tolterodine ER 4 mg (n=495)
		25 mg (n=432)	50 mg (n=1375)	100 mg (n=929)	
Overall 12 Week Phase 3	658 (47.7%)	210 (48.6%)	647 (47.1)	402 (43.3)	231 (46.7)
Overall Long Term Study		(n=812)	(n=820)		(n=812)
		213 (26.2)	192 (23.4)		224 (27.6)

Source: Tables 5.2.3.1 and 5.5.1.4 ISS/SCS

There does not seem to be an increase in adverse events over time with mirabegron use. In Study 178-CL-049, 18.7% of patients enrolled had not participated in Studies 178-CL-046 or -047. It would be expected that they would have an increased number of AEs in association with exposure to either mirabegron or tolterodine. Even with that consideration the incidence of TEAEs in Study 178-CL-049 was lower than in the pooled pivotal studies.

This reviewer is not aware of any analysis with regard to time to resolution of adverse events once study drug is terminated.

It is noted that in the Phase 3 trials, the small number of clinical AEs of increased serum liver function tests were reported at around Day 56.

7.5.3 Drug-Demographic Interactions

Race/Ethnicity

The Japanese phase 2/3 studies had higher proportions of patients with abnormal laboratory AEs, since any abnormal value representing at least a 20% worsening from baseline was required by protocol to be reported as a clinical AE.

Within the phase 3 studies, no apparent differences by race were observed; however, due to small numbers of non-White and non-Asian patients in the phase 2/3 studies, conclusions regarding TEAEs by race cannot be drawn.

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); thus, there were too few Hispanic or Latino patients to effectively evaluate comparisons based on ethnicity.

Reviewer's Comment: There were too few patients of races other than white to draw safety conclusions based on race.

Gender

The frequency of TEAE was generally higher in female patients compared with male patients across treatment groups in the 12-week studies, and generally similar in the long-term studies. The difference from placebo was similar between genders. Women comprised approximately 70 % of the subjects in the phase 3 studies. The overall incidence of TEAEs by gender in the Phase 3 studies were:

Table 91: TEAE by Gender 12 Weeks Pivotal Studies

MedDRA v12.1 (n%) of Patients	Placebo (n=1380)	Mirabegron			Tolterodine ER 4 mg (n=495)
		25 mg (n=432)	50 mg (n=1375)	100 mg (n=929)	
Overall TEAE	658 (47.7%)	210 (48.6%)	647 (47.1)	402 (43.3)	231 (46.7)
Women					
	(n=1002)	(n=292)	(n=982)	(n=675)	(n=361)
Overall TEAE	487 (48.6)	147 (50.2)	466 (47.5)	303 (44.9)	166 (46.0)
Men					
	(n=378)	(n=139)	(n=393)	(n=254)	(n=134)
	171 (45.2)	65 (45.3)	181 (46.1)	99 (39.0)	65 (48.5)

Source: Table 5.2.3.2.1, ISS

Reviewer's Comment: The frequency of TEAE was generally higher in female patients compared with male patients across treatment groups in the 12-week studies, and generally similar in the long-term studies. The differences between mirabegron and placebo are not different by gender. The frequency of hypertension was observed more in male than female patients, but the differences between mirabegron and placebo were no different for men versus women. No dose adjustment is deemed necessary by gender despite differences in exposure by gender.

Age

In the OAB 12-week Phase 3 Population, the frequency of TEAEs reported was higher in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups. For mirabegron, the difference from placebo or from tolterodine was generally similar between age groups.

Table 92: Incidence of Overall TEAEs by Age Group (< 65, ≥ 65 years) Phase 3 Studies

Age MedDRA (v12.1) n (%) Patients	Placebo	Mirabegron				Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	Total	
<65years	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
<65years	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)

Source: ISS Table 5.2.3.2.2

In the EU/NA Long-term Controlled Population, the frequency of TEAEs reported was higher in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups. For mirabegron, the difference from tolterodine was similar across age groups.

Table 93: Incidence of Overall TEAEs by Age Group (<65, ≥65 years) Long-term Controlled Population

Age MedDRA (v12.1) n (%) Patients	Mirabegron			Tolterodine ER 4 mg
	50 mg	100 mg	Total	
<65years	N= 523	N= 504	N= 1027	N= 509
≥65 years	N= 289	N= 316	N= 605	N= 303
Overall rate	485 (59.7)	503 (61.3)	988 (60.5)	508 (62.6)
<65years	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)

Source: Table 168, ISS, page 334.

In the 12-week and long-term studies, the frequency of SAE was higher in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups; however there was no evidence of a mirabegron effect by age. In the 12 weeks studies, the frequency of SAEs in mirabegron 25 mg and mirabegron 50 mg subjects was 1.8% and 1.7% as compared to 1.6% for placebo subjects in the <65 year old group. In the 12 weeks studies the frequency of SAEs in

mirabegron 25 mg and mirabegron 50 mg subjects was 1.3 % and 2.7% as compared to 2.9 % for placebo subjects in the ≥ 65 year old group.

In the EU/NA Long-term Controlled Population, the frequency of SAEs was higher in patients ≥ 65 years of age compared with patients < 65 years of age, but there was no significant differences between treatment groups for either age group. The percent overall incidences for the <65 year old group was 4.6 % for mirabegron 50 mg, 4.4% for mirabegron 100 mg and 4.3% in the tolterodine group. The percent overall incidences for the ≥ 65 year old group were 6.2% for mirabegron 50 mg, 9.2% for mirabegron 100 mg and 7.3% in the tolterodine group. The most common SAE in the total mirabegron group were gastritis (mirabegron: 2/1027 [0.2%]; tolterodine: 0/509), liver function test abnormal (mirabegron: 2/1027 [0.2%]; tolterodine: 0/509) and osteoarthritis (mirabegron: 2/1027 [0.2%]; tolterodine: 0/509) in patients < 65 years of age and abscess intestinal (mirabegron: 2/605 [0.3%]; tolterodine: 0/303), atrial fibrillation (mirabegron: 2/605 [0.3%]; tolterodine: 3/303 [1.0%]) and prostate cancer (mirabegron: 2/605 [0.3%]; tolterodine: 0/303) in patients ≥ 65 years of age.

Reviewer's Comment: In 12-week and long-term studies, the reported frequency of TEAE was higher in patients ≥ 65 years of age compared with patients < 65 years of age across treatment groups. In 12-week Phase 3 Population and the EU/NA Long-term Controlled Population, TEAE were generally reported more frequently in patients ≥ 65 years of age compared with patients < 65 years of age, but there were no differences across treatment groups. There did not seem to be a dose effect.

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 OAB 12-week Phase 3 Population and 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 12-week and long-term studies, 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. In the total mirabegron group, the discontinuation rate was 5.8% for <75 years of age and 7.7 % for patients ≥ 75 years of age in the long-term study.

Reviewer's Comment: There is a modest increase in adverse events leading to discontinuation in elderly patients, but no evidence of a treatment or dose effect.

BMI

In the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations, the overall frequency of TEAE generally increased with increasing BMI.

BPH

Subgroup analysis based on presence or absence of history of BPH for male patients was performed because patients with BPH are at risk for urinary retention. Although the rates of UTI were generally higher in male patients with BPH history compared with males without BPH, the pattern of comparisons between treatment groups was similar to that observed in the overall population, suggesting that these patients are not at increased risk of UTI with mirabegron treatment. There were no notable differences between the patients with or without a history of BPH in change from baseline to final visit in PVR volume.

Geographic Region

The frequency of TEAE was generally higher in North America compared with Europe across treatment groups in both the 12 weeks studies and the long term studies.

Prior OAB Medication

The overall frequency of TEAEs was higher in patients with prior OAB medication history compared to patients with no prior OAB medication in both the 12 weeks and long-term studies. In the 12 weeks studies, the overall discontinuation frequency was higher in patients with a previous OAB medication history while in the long term study it was not.

7.5.4 Drug-Disease Interactions

Glucose Metabolism: Based upon the potential for beta adrenergic agonist to affect glucose metabolism, this area was explored. In the EU/NA OAB 12-week Phase 3 Population, one or more hypoglycemia TEAEs was reported by 2/2736 (0.1%) mirabegron patients and 1/1380 (0.1%) placebo patient; no (0/495) tolterodine patients experienced a hypoglycemia TEAE. There were no SAE reports of hypoglycemia. In the Long-term Controlled Population no patient reported hypoglycemia.

In the EU/NA OAB 12-week Phase 3 Population, one or more hyperglycemia TEAEs was reported by 25/2736 (0.9%) mirabegron, 13/1380 (0.9%) placebo and 3/495 (0.6%) tolterodine patients. The incidence of treatment emergent diabetes including subtypes (Higher level term) was 0.4% for placebo, 0.4% for total mirabegron [0.5% for mirabegron 50 mg] and 0.4% for tolterodine.

Reviewer's Comment: With mirabegron doses up to 100 mg daily in the study population, hypoglycemia and hyperglycemia were rare and do not appear to be safety issue.

In Phase 3 studies, mirabegron raises the blood pressure by 1 mmHG and the pulse by 1-2 beats per minute. The potential impact of these vital sign changes on cardiovascular outcomes has been discussed in previous sections of this review.

7.5.5 Drug-Drug Interactions

For a detailed review of potential drug-drug interactions (DDI), the reader is referred to the Clinical Pharmacologist's review, as well as to previous sections of this review. Mirabegron-related DDI is briefly summarized here as well.

Mirabegron is cleared by multiple mechanisms (metabolism, renal and possibly biliary excretion) and drug-metabolizing enzymes, with no single predominating clearance pathway. A number of interaction studies with compounds affecting CYP3A and P-gp, as well as with products affecting renal secretion, and with other urologic products, were performed in healthy subjects. PK measures indicating the magnitude of the effect of coadministered drugs on mirabegron pharmacokinetics were determined. The largest changes in mirabegron plasma exposure were observed during co-administration with potent modulators of CYP3A and P-gp. 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 qd). Co-administration 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 qd). These results, in the Sponsor's opinion, indicate that mirabegron is not a sensitive substrate for CYP3A4 *in vivo*. No dose adjustment is needed for mirabegron when co-administered with ketoconazole, rifampin or other modulators of CYP3A or P-gp in the Sponsor's opinion.

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. The Sponsor concludes that no dose adjustment is needed for mirabegron when co-administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolizers.

Mirabegron PK was not affected to a clinically significant extent by metformin, solifenacin or tamsulosin. In addition, there was no clinically relevant pharmacodynamic (PD) interaction between tamsulosin and mirabegron. As a result, no dose adjustment for mirabegron is necessary when combined with these drugs.

With regard to specific drugs and the effects of mirabegron on their pharmacokinetics the Sponsor makes the following observations:

- Multiple qd dosing of 100 mg mirabegron 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 PK of desipramine was measured. Drugs that are CYP2D6 substrates are not expected to require dose adjustment, except for drugs significantly metabolized by CYP2D6 with a narrow therapeutic index. Caution is advised if mirabegron is co-administered with such drugs.

- Mirabegron (100 mg qd) did not affect the pharmacokinetics of ethinyl estradiol and levonorgestrel (both CYP3A4 substrates; combined oral contraceptive). No dose adjustment for these co-administered drugs is necessary.
- Mirabegron (100 mg qd) did not affect the pharmacokinetics of solifenacin (a CYP3A4 substrate) to a clinically significant extent. No dose adjustment is necessary if this drug is co-administered.
- Mirabegron (100 mg qd) increased plasma exposure of the CYP2D6 and CYP3A4 substrate tamsulosin (0.4 mg sd) by approximately 60%. The cardiovascular results do not suggest a clinically relevant PD interaction between tamsulosin and mirabegron. There was no change in systolic blood pressure (SBP) and a small decrease in diastolic blood pressure (DBP) during coadministration of mirabegron and tamsulosin compared to tamsulosin alone. No dose adjustment is necessary if this drug is co-administered.
- 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 co-administered with warfarin (25 mg qd). No dose adjustment for these co-administered drugs is necessary.
- Plasma exposure of metformin (500 mg bid) was not changed to a clinically relevant extent by mirabegron co-administration (160 mg IR qd). As a result, no dose adjustment for these co-administered drugs is necessary.
- 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%. 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 for and used to titrate the digoxin dose in order to obtain the desired clinical effect.

Reviewer's Comment: While we defer to clinical pharmacology in these matters, the Sponsor recommends that drugs with a narrow therapeutic index and that are significantly metabolized by CYP2D6 should be cautiously administered in association with mirabegron use. Digoxin, a P-gp substrate, should be administered at the lowest dose and upwardly titrated based upon serum concentrations. These recommendations appear reasonable.

Beta Blockers at Baseline

The clinical trial safety results for the use of beta blockers at baseline do not identify a potential safety concern, in my opinion.

Alpha 1-AR Antagonists at Baseline

In the 12 week studies, the incidence of clinical adverse event reports of “hypertension” was higher in patients using alpha 1 –AR blockers at baseline compared to those not using alpha 1-blockers at baseline (Table 202, ISS, page 394). A higher incidence of “hypertension” AEs was also noted in the 100 mg subjects in the long-term study (Study 049) in subjects using alpha 1 –AR blockers at baseline compared to those not using alpha-1 AR blockers at baseline. The use

of alpha 1 –AR blockers at baseline was associated with a lower frequency of TEAE in the total mirabegron group and placebo groups in both the 12 weeks and long term studies. The frequency of SAEs and TEAEs leading to discontinuation was higher in both the 12 weeks and the long term study in patients using alpha 1 –AR blockers at baseline than in patients who were not using alpha-1 AR blockers at baseline (long term study: 10.6 % versus 4.8% in the mirabegron 50 mg group and 10.2% versus 6.0% in the mirabegron 100 mg group. In the tolterodine group the results were 6.3% versus 5.4% [Table 205, ISS, page 397]). The findings were similar in the 12 weeks studies.

Reviewer's Comment: The increased incidence of adverse events in patients using alpha-1 blockers at baseline appears to be a reflection of inherent increases in adverse events for alpha 1-AR blockers themselves, not an interaction with mirabegron.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The reader is referred to the previous sections of this review, where the increased incidence of neoplasm SAEs, as well as new malignant events, in the 12-Week and Long-Term studies are discussed. Animal studies did not demonstrate carcinogenicity or mutagenicity with mirabegron. No other safety evaluations were conducted for human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies using mirabegron in pregnant women. No embryo-fetal toxicity was observed in rats at systemic exposures that were 6.2-fold higher than the human systemic exposure at the MRHD. An increased incidence of a skeletal anomaly and variation (wavy rib) was observed at systemic exposures that were equal to or greater than 21.5-fold the human systemic exposure at MRHD. These findings were reversible.

No embryo-fetal toxicity was observed in rabbits at systemic exposures that were 0.7-fold the human systemic exposure at the MRHD. The embryo-fetal no observed adverse effect level (NOAEL) was established in this species based on reduced fetal body weight observed at systemic exposures that were 14.1-fold higher than the human systemic exposure at MRHD. At still higher doses, where systemic exposures were 35.7-fold higher than the human exposure at MRHD, 1 of 17 pregnant rabbits died, and fetal findings of dilated aorta and cardiomegaly were reported. The frequency of these findings was reduced by coadministration of the beta 1-AR antagonist, metoprolol.

Nonclinical studies indicate that mirabegron is excreted in the milk of rodents and therefore is predicted to be present in human milk. No studies have been conducted to assess the impact of

mirabegron on milk production in humans, its presence in human breast milk or its effects on the breast-fed child.

Mirabegron is classified as Pregnancy C. The Sponsor states that the use of mirabegron in pregnancy should be avoided unless the benefit to the patient outweighs the risk to the fetus. The Sponsor also states that mirabegron should not be administered during nursing unless the potential benefit to the patient outweighs the potential risk to the neonate.

According to the 120 Day Safety Update, a total of 9 pregnancies have been reported in subjects enrolled in mirabegron clinical studies. Narratives in brief are presented below:

- Patient No. 178-CL-049, 3063-3438, a 27-year-old woman treated with mirabegron 50 mg, completed suicide through overdose with anxiolytics and antidepressants and pregnancy was confirmed on autopsy. Death occurred 93 days after the last study drug kit was dispensed at the month 9 visit (day 267, nontreatment-emergent).
- Patient No. 178-CL-049, 3138-2469], a 28-year-old woman discontinued treatment with mirabegron 50 mg on day 218 due to pregnancy; at 225 days after the last study drug exposure (38 weeks gestation), the patient gave birth to a male infant. The patient had also been taking lamotrigine to treat her epilepsy. It was reported that no congenital malformation due to the patient's lamotrigine exposure was observed. Prior to discharge, the male infant was diagnosed with cryptorchism, which was considered by the Sponsor as serious and medically significant. As per the Sponsor's medical assessment, gestational exposure to mirabegron was limited to the first trimester for a total of approximately 33 days.

Reviewer's Comment: First trimester exposure to mirabegron is unlikely to affect testicular migration that typically occurs during the eighth month of gestation.

- Patient No. 178-CL-046, 3224-3015, a 44-year-old woman treated with mirabegron 50 mg, reported a pregnancy on day 49. Pregnancy was terminated with elective abortion.
- Patient No. 178-CL-059, E0171701-2014, a 32-year-old female volunteer given mirabegron 100 mg and digoxin in a drug interaction study, reported a pregnancy on day 30. Pregnancy ended with elective abortion.
- Patient No. 178-CL-076, U00022981233, a 29-year-old female volunteer given mirabegron (intravenous dose of 15 mg and 3 single oral doses of mirabegron 100 mg over 31 days, each dose separated by a 10-day washout) in a Phase 1 study, reported a pregnancy on day 46. Pregnancy ended with spontaneous abortion.
- Patient No. 178-CL-081, U00029421046, a 34-year-old female given placebo in the ocular safety study, reported a pregnancy on day 55. The patient had a twin pregnancy and experienced spontaneous complete abortion of 1 of 2 gestational sacs. Pregnancy with the other fetus was reported as ongoing.
- Patient No. 178-CL-081, U00029421122, a 37-year-old female given mirabegron 100 mg in the ocular safety study, reported a pregnancy on day 55. Pregnancy was reported as ongoing.

- Volunteer No. 178-CL-077, 0885-1183, a 31-year-old male volunteer given placebo (period 1) and mirabegron 100 mg (period 2) in a thorough QT study reported the pregnancy of his partner to the Investigator (on 27 October 2011) after the birth of his child (born [REDACTED]^{(b) (6)}) several months after completion of study conduct. Based on the last dose of study medication on day 35 (18 October 2010), the subject was instructed to continue the use of contraceptive medication through 18 November 2010. Based on the gestational period, the subject and his partner had an estimated conception date between 06 November 2010 and 11 November 2010 (19 to 24 days after last dose of study medication). The subject's partner had no reported abnormalities during pregnancy and gave birth to a live full-term male infant with no reported abnormalities. This event of pregnancy was considered an SAE.

Reviewer's Comment: It would appear that patient was not on study drug at the time of his partner's conception by my analysis.

- Patient No. 178-CL-100, 42106-10076, a 37-year-old woman (gravida 2, para 2) treated with blinded study medication in an ongoing study, was found to have a positive human chorionic gonadotropin (hCG) test after 7 days of exposure to study drug treatment i. Study drug was immediately discontinued and 25 days later the patient experienced a spontaneous abortion (gestation duration 5 weeks and 3 days). The patient was hospitalized for uterine bleeding and underwent an uncomplicated instrumental revision of the uterus with subsequent recovery and discharge to home.

Reviewer's Comment: This patient, in my opinion, had conceived prior to drug exposure. The study has a 2 week single-blind run-in period followed by 12-week double-blind treatment period with 9 treatment arms. 2 arms contain solifenacin only and one additional arm contains solifenacin with either mirabegron 25 mg, mirabegron 50 mg or placebo. The study is listed as ongoing in the 120 Day Safety Update and it is therefore possible the patient did not receive mirabegron. In a narrative December 2011, the Sponsor states that the both the pregnancy and the spontaneous abortion occurred while the patient was not on any active treatment. This patient was also exposed to lamotrigine for epilepsy.

In summary, one of the 9 reported pregnancies occurred in a placebo subject and resulted in the spontaneous abortion of 1 fetal sac (the patient was pregnant with twins). One pregnancy occurred in a female partner of a male taking mirabegron, and it resulted in a normal birth and normal child. One pregnancy and spontaneous abortion occurred in a patient in an ongoing blinded study who was also taking an anti-epileptic drug. One mirabegron patient pregnancy occurred in patient with previous history of spontaneous abortion and resulted in a spontaneous abortion. One pregnant mirabegron patient successfully completed suicide. Two mirabegron patients terminated their pregnancies with elective abortions. One pregnancy, in a patient with mirabegron exposure (for 33 days in the first trimester) and exposure to an anti-epileptic drug, resulted in an infant with bilateral cryptorchid testes.

Reviewer's Comment: Several spontaneous pregnancies and abortions (both spontaneous and elective) may be expected in a large female study population.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no pediatric studies or assessment effects on human growth in this submission. Prior to conducting pediatric studies, the Sponsor will be asked to conduct juvenile animal studies to be assured of safety regarding bone maturation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

While there is no information on massive overdosage of mirabegron, there is clinical trial data for fairly large, supraphysiological doses. Phase 1 studies showed a dose-related increase in blood pressure and pulse rate. Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and SBP when administered to healthy volunteers. At a daily dose of 200 mg in female volunteers, the placebo-subtracted, change-from-baseline in QTc interval modestly broached the regulatory standard for no evidence of QT prolongation (90% CI 13.4 msec compared to 10 msec). The Sponsor recommends treatment for overdosage should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure and ECG monitoring are recommended. There were no AEs 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.

Review's Comment: The results from the QT studies, including the finding in women at a dupraphysiological dose of 200 mg daily should be included in the drug label.

Beta 3-ARs are not amongst the CNS receptors known to mediate abuse-related effects. Evaluation of the clinical data in the mirabegron program suggests that mirabegron is unlikely to demonstrate abuse potential. Among the 5863 patients who received at least one dose of mirabegron in phase 2/3 studies, there were no reported AE suggesting a risk of abuse liability.

In both the nonclinical and clinical mirabegron studies, there is no evidence of withdrawal or rebound. There were no AE with the PT of drug withdrawal syndrome or withdrawal syndrome among the 5863 patients who received at least one dose of mirabegron in phase 2/3 studies.

The Sponsor did not find an indication in either the preclinical or clinical studies that mirabegron affects the ability to drive or operate machinery, or impairs mental ability. Dizziness, somnolence and blurred vision were only reported in several patients amongst several thousand treated with mirabegron.

7.7 Additional Submissions

8 Postmarket Experience

Mirabegron was approved for marketing in Japan (trade name; Betanis) on July 1, 2011. As of February 10, 2011, 37 written IND safety reports for suspected, unexpected, serious adverse reactions (SUSAR) for YM178 (mirabegron) have been submitted to IND 69416 in accordance with 21 CFR 312.32. The total number of patients using Betanis is not known. It is to be noted that mirabegron is marketed at the 25 and 50 mg doses in Japan. The usual recommended dose is 50 mg and the 25 mg dose of mirabegron is to be used in patients with moderate hepatic function disorder or patients with severe renal impairment according to the label. Because of demographics, the drug exposure is considerably higher than in EU/NA patients. This may make the adverse event profile for mirabegron different than that seen in this NDA application. Below is a table summarizing the received safety reports as of February 9, 2012:

Table 94: Japan Postmarketing Adverse Events for Mirabegron

Report Number, Sex, & Age	Betanis Dose (YM178)	Exposure Days to Event	Event	Event Outcome	Other Information
2011JP007650 Male, 70	50 mg	Not stated	Retention	Not stated	History of BPH
2011JP008088 Male, ?age	Not stated	Not stated	Retention	Not stated	
2011JP008433 Male, 66	50 mg	10 Days	Retention 900 cc	Continuing Self-cath	Hx BPH Hx Was on silodosin
2011JP008595 Male, 84	25 mg	Not Stated	Retention 400cc Hydronephrosis, Acute Renal Failure	Unknown	Diabetic On Tamsulosin Hx BPH
2011JP009147 Male, 83	50 mg	1 Day	Retention	Sent to Hospital	Hx BPH
2011JP009271 Male, ?age	50 mg	1 Day	Retention	Catheter- resolved	Reclassified Dysuria
2011JP009290 Male, ?age	Not stated	Not stated	Retention	Not stated	
2011JP009597 Male, “60s”	Not stated	Not stated	Retention, 1050cc Recath 850cc	Not stated	On Vesicare BPH
2011JP009618 Male, 80	50 mg	Day 47	Retention Catheterized in Hospital	“Recovering”	Solefenacin Day 28 and increased Day 40

Clinical Review
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 {Insert Product Trade and Generic Name}

2011JP009612 Male, ?age	50 mg	Not stated	Retention	Dechallenge "positive"	
2012JP000430 Male, ?age	25 mg	Not stated	Retention	Not stated	Hx BPH
2012JP000588 Male, "80s"	Not stated	Not stated	Retention Catheterization	After catheterization "recovering"	BPH on solifenacin and silodosin
2011JP007411 Female, 77	50 mg	Day 2	Retention Catheterization	Recovered	Corrected to dysuria
2011JP007486 Female, 75	50 mg	Day 4	Retention 400cc by catheter	Not stated	
2011JP00527 Female, ?age	25 mg	Not stated	Retention Catheterized	Recovered	
2012JP000319 Female, 82	50 mg	Day 3	Retention	Not stated	PVR 300CC Day 1
2012JP000594 Female, ?age	50 mg	Day 14	Retention	Treatment discontinued, "recovered same day"	On solefenacin
2011JP009681 Female, 84	50 mg	Day 20	Retention, PVR 140cc Edema	Recovered after mirabegron discontinued	On Vesicare (among 10 meds), Hx cerebral infarct, Tbc
2011JP007506 Male, 73	50 mg Reduced to 25 mg unknown day	11 Days & 13 Days	Chest Pain- possible acute coronary syndrome	"dechallenge positive"	Pyrexia also reported
2011JP007567 Female, ?age	50 mg	Not stated	Arrhythmia (no further detail)	Hospitalized Recovered	Unknown history
2011JP009336 Female, 92	50 mg	Day 6	Arrhythmia ST depression CV ischemia suspected	Recovered	Diabetic
2011JP009653 Male, 68	50 mg	Day 5	Ventricular tachycardia	Event Resolved	Dilated Cardiomyopathy Tachycardia, CVA by history
2012JP000177 Male, 82	50 mg	Day 1	Chest pain (spastic angina) Positive	Symptoms resolved with dechallenge	History hypertension, BPH

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			rechallenge		
2012JP000585 Female, 69	50 mg	Day 11	Cardiac Failure	Outcome unknown By Day 23 weight normal	BNP 180.2 No cardiac history. Diabetic, hyperlipidemia
2011JP007679 Female, 73	50 mg	Day 1	Erythema Multiforme	Recovered	Mild rash prior to mirabegron
2011JP008642 Female, 86	50 mg	Day 2	Erythema Multiforme	Recovered	Mild rash prior to mirabegron
2011JP009662 Female, 82	Not stated	Day 3	Increased CPK	Dechallenge Positive	
2011JP008795 Male, 76	50 mg	Day 4	Myalgia, Rhabdomyolysis CPK 7000	Not stated	
2011JP008630 Male, 86	50 mg	Day 4	Orange/Brown urine	Day 10 drug stopped and recovered	Similar episodes prior to mirabegron
2011JP009536 Female, 71	50 mg	Day 7	Retinal vein occlusion	Not recovered as of Day 28	
2011JP007445 Female, ?age	Not stated	Not stated	Anosmia	Unknown	
2011JP008357 Female, 76	50 mg	Day 2	Hallucinations	Not recovered as of Day 6	Parkinsons on pramipexole and selegilene
2011JP007751 Male, 83	50 mg	Day 9	Progression of macular degeneration	Not stated.	Macular changes antedate mirabegron
2012JP000245 Male, 71	50 mg	Day 3 (approximate)	Increased PVR (32-220), incontinence worse	Event resolved Day 15	BPH
2012JP000596 Male, 78	50 mg	Not stated	Hyperglycemia	Resolved with Medication resumption	Pt stopped oral agents for diabetic control, Hepatic steatosis
2012JP000013 Male, 73	25 mg	Day 3	Vomiting, Nausea	Recovered while on mirabegron	Hx chronic renal failure and gastritis, DM, intestinal

					obstruction
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Source: Manufacturer reports to IND 69416 The shaded events have short narratives below.

Of the 37 reported cases in Table 95, selected cases are presented in brief narrative form:

Ventricular Tachycardia (2011JP009653): This 68 year old male had a history of loss of consciousness prior to starting mirabegron. The medical history includes dilated cardiomyopathy, tachycardia, cerebral infarction and hypertension. The patient was taking Norvasc. The patient started mirabegron 50 mg on 16 December 2011. On [REDACTED] (b) (6) he was also prescribed paroxetine. At 4 PM on that day, he noted palpitations. He was seen at a clinic at 5:30 PM and was admitted to hospital with tachycardia. At the time of hospital arrival, the blood pressure was 80-100 mm Hg by palpation and the heart rate was 238 bpm. A defibrillator was used once (100J). He was then treated with amiodarone and his symptoms improved. Coronary angiography on [REDACTED] (b) (6) detected no significant stenosis. During this adverse event no prolonged QT was observed, ventricular extrasystoles were observed and ST-T changes were observed in V5 and V6 (inverted T waves). Echocardiography revealed mild left ventricular hypertrophy and mitral valve regurgitation “grade 1.” BNP was 682 and was 181 on 27 January 2012.

Reviewer’s Comment: This case is confounded by pre-existing medical history and recent addition of paroxetine which makes attribution to mirabegron problematic.

Chest Pain-possible acute coronary syndrome (2011JP007506): This 73 year old male with a medical history of hypertension, hyperlipidemia, cerebral infarction and reflux esophagitis. In the past he had tuberculous pleurisy and surgery for a spinal cord tumor and a right adrenal adenoid tumor. Concomitant medication was tizanalin (a muscle relaxant). 11 days after starting mirabegron 50 mg, after eating dinner, chest pain developed which spontaneously subsided. Chest pain reoccurred 2 days later in the morning and again subsided. On the same day in the evening chest pain reoccurred and the patient visited his physician. The blood pressure was 196 mmHg systolic and 100 mm Hg diastolic with a pulse of 96 bpm. The patient was treated with 10 mg of nifedipine and put to rest without pain improvement. He was then seen in the hospital emergency department. He reported chills with a temperature of 37 degrees centigrade. ECG revealed T-wave inversion (negative T-waves) in leads aV1 and from V3 to L. The white blood cell count was elevated as was the C reactive protein. Mirabegron was discontinued, the patient admitted to the hospital and treatment with oral spray and intravenous nitroglycerin begun. One day after admission the patient was considered to have recovered from the event. The causes of pyrexia and increased inflammation could not be determined.

The patient had had chest pain in the past but not pain with similar time course.

Reviewer’s Comment: The patient was taking mirabegron for 11 days before the acute event. He had a past history of hypertension without concurrent active treatment, but Sponsor states on a unspecified date the diastolic blood pressure was 100 mmHg. It appears that the event occurred in association with pyrexia, increased white blood cell count. a temporary rise of the blood pressure and an increase in pulse rate. The

underlying diagnosis and reason for the event is not clear. The role of mirabegron in this event is also unclear.

Arrhythmia (no further detail) 2011JP007567: This female of unstated age started mirabegron 50 mg on an unknown date. On an unspecified date, the patient was hospitalized for an arrhythmia of unspecified type. In a followup report, the patient is described as recovered with no additional details.

Angina Pectoris (2011JP009336): This 92 year old female took mirabegron 50 mg on November 30, 2011 through December 6, 2011. The patient's medical history includes diabetes mellitus, dyslipemia and bladder cancer. On 6 December 2011, the patient developed jaw pain. ECG changes were ST segment depression in V3-V6. Angina pectoris was suspected and patient was treated with intravenous nitroglycerin. By 7 December 2011, the ECG changes were no longer present. On 13 December 2011, the patient is described as recovering and is no longer using nitroglycerin. She continues on diltiazem. The report does not contain any pulse or blood pressure data.

Reviewer's Comment: The event occurred after 6 days of mirabegron treatment in a 92 year old subject with no past history of cardiac disease. The vital signs data is not available. The role of mirabegron in the event is unclear.

Chest Pain (2012JP000177): This 82 year old male patient has a medical history that includes reflux esophagitis, hyperlipemia, angina pectoris and alcohol use. His concomitant medication is telmisartan [solifenacin stopped 29 October 2011 secondary to dry mouth]. The patient started mirabegron 50 mg on (b) (6). On the same date, the patient developed chest pain and mirabegron was discontinued (b) (6). Cardiac catheterization revealed 50% stenosis of segment 7 of left anterior descending coronary artery. It was determined that the chest pain was a symptom of coronary spastic angina. When mirabegron treatment was stopped, the chest pain was subsided. He was started on aspirin, diltiazem and atorvastatin. Solifenacin was resumed. On (b) (6) after having resumed mirabegron (date unknown), the chest pain reoccurred. No chest pain was observed at hospital. Mirabegron was discontinued.

Reviewer's Comment: The recurrence of chest pain after resuming mirabegron could suggest a causal relationship, but the patient's background condition of coronary artery disease, reflux esophagitis and angina pectoris makes attribution problematic.

Cardiac Failure (2012JP000585): This 69 year old male was treated with mirabegron 50 mg from 26 December 2011 until 6 January 2012. The patient had no history of cardiac disease but was a diabetic and had hyperlipemia. He was also taking naftopidil (an alpha-1 receptor antagonist). On (b) (6), the patient developed cardiac failure with weight gain of 5 kg and facial edema. The brain natriuretic peptide was 180.2 (units not stated). On January 18, 2012, the patient's weight returned to normal. There is no detail of treatments or diagnostic tests performed.

Reviewer's Comment: Information is insufficient for analysis. Co-morbidity and concomitant medications further confound an assessment of causality.

Erythema Multiforme (2011JP007679): The patient is a 73 year old female who received mirabegron therapy from 14 October 2011 to 19 November 2011. The patient was not taking concomitant medication and had no prior history of allergies or drug allergies. Prior to initiation of therapy, the patient was noted to have a rash (location not specified) “so mild as to pose no problem.” On 15 November, 2011, the patient developed generalized erythema which progressed to involve the entire body excepting the face. No skin exfoliation was observed. There were no symptoms such as fever, arthralgia, swollen lymph nodes, shortness of breath, angioedema, blood pressure decrease, blister/bullous lesions or mucosal erosion. The lesions were not photographed. No laboratory tests results are reported. The patient was treated with topical and oral steroids. She was not hospitalized and recovered from the event.

Reviewer’s Comment: The diagnosis of erythema multiforme can not be confirmed in this case due to lack of detail.

Erythema Multiforme (2011JP008642): The patient is a 86 year old female who started mirabegron 50 mg on 14 October 2011 and continued on the medication until 19 November 2011. Prior to initiation of therapy, the patient was note to have a rash (site not specified) “which was so mild as to pose little problem.” On 15 November, 2011, the rash had spread all over the body and the patient developed generalized erythema. The patient was not taking concomitant medication and did not have a history of underlying disease or allergic disposition based on the manufacturer’s report. The patient responded to oral and topical steroidal therapies.

The report does not contain mention of skin exfoliation, fever, arthralgia, swollen lymph nodes, shortness of breath, angioedema, blood pressure decrease, blister/bullous lesions or mucosal erosion. There is no mention of a lesion photograph. No laboratory tests results are reported.

Reviewer’s Comment: There are similarities between the two previous cases and the dates of starting drug are identical. The dates of the adverse event are also almost identical. These may represent 1 case.

Reviewer’s Comment: Rare but serious hypersensitivity reactions were reported in the clinical development program. It is not entirely clear that any of these reactions were directly related to mirabegron, although the role of mirabegron cannot be ruled out. It would be reasonable to have a Postmarketing section in labeling and to include some of the reported events (e.g. urinary retention). The episodes of urinary retention in some patients, especially those taking anti-muscarinics and in men with BPH, are notable.

9 Appendices

9.1 Literature Review/References

Literature references were provided by Sponsor and were reviewed as needed during the review of the application.

9.2 Labeling Recommendations

Clinical labeling recommendations were provided throughout the review, but especially at the time of labeling discussions with the entire review team and with the Sponsor.

9.3 Advisory Committee Meeting

On April 5, 2012, an Advisory Committee was convened to discuss the safety and efficacy of mirabegron as a new molecular entity. The major topics including the efficacy of the product, the blood pressure effects, the increased incidence of neoplasms at the 100 mg dose, the hepatic adverse events and hypersensitivity reactions. At the April 5, 2012, Advisory Committee meeting the Division tasked the committee to answer three questions which are shown below along with Committee responses:

1. Do the data provide substantial evidence of benefit for mirabegron in the treatment of overactive bladder? (**VOTING QUESTION**) *Committee voted Yes 8, No 4 and Abstain 0*
 - a. If you vote “No”, provide a rationale. *In general, those who voted no stated that the endpoints were met but nonetheless they did not view the clinical benefit as “substantial.”*
2. Has adequate safety been demonstrated for mirabegron in the treatment of overactive bladder? (**VOTING QUESTION**) *Committee voted Yes 9, No 3 and Abstain 0*
 - a. If you vote “No”, provide a rationale. *Of the 3 committee members who voted no, Dr. Gillen continued to voice a concern about dose selection re: efficacy, Dr. Garnick voiced concerns regarding potential cardiovascular and cancer risks, and Dr. Orza stated her agreement with Drs. Gillen and Garnick. Among those who voted Yes, reservations and caveats were expressed in regard to the blood pressure and heart rate effects, and some concerns were voiced with regard to hepatic adverse events and hypersensitivity reactions. The Committee members who voted “Yes” generally encouraged postmarketing “monitoring” and postmarketing studies, especially a more robust cardiovascular safety study.*
3. Considering all the available data, including information from the briefing documents and today’s discussion, does the overall benefit-risk assessment support approval of

mirabegron for the treatment of overactive bladder? **(VOTING QUESTION)** *Committee voted Yes 7, No 4, Abstain 1*

- a. If you vote “No”, provide a rationale and recommendations for resolving outstanding concerns. *For those 4 committee members who voted “No”, the following was provided as rationale: Dr. Orza stated an “underwhelming” treatment effect and “concerning” safety signals. She stated that if the drug was approved, it should have careful labeling and postmarketing monitoring. Dr. Garnick said the decision was difficult because some data analyses were inadequate. He stated “marginal” efficacy was demonstrated and he did not yet have a full understanding of safety. Dr. Gillen reiterated his recommendation that 25 mg appears to be the target dose. Ms. Chauhan stated concerns related to lack of data in African American patients and the cardiovascular and cancer risks.*

- b. If you vote “Yes”, provide a rationale and if applicable, additional recommendations. *Of the committee member voting “Yes”, in regard to benefit, one stated the need for new medications for the treatment of OAB, one stated that the effects seemed comparable to what is currently available for the condition, one stated that some patients will derive benefit, and one stated “marginal” but sufficient efficacy. In regard to safety, postmarketing “monitoring” and “studies” were encouraged, one member stated that a starting dose of 25 mg would be reasonable for efficacy and safer than 50 mg, and some members advised careful labeling (e.g., one member suggested a caution for use in patients with severe levels of hypertension).*

On May 3, 2012, in a teleconference, the Division informed the Sponsor that pending a DEPI consultation evaluating the proposed Observational Cardiovascular (CV) Cohort Study (Sponsor will submit a more detailed outline), their plan to evaluate CV risk in the post marketing period appears satisfactory. The Sponsor was agreeable to the Division’s recommendation to further study the association of mirabegron and malignancy in the post marketing period and proposed an observational cohort approach. A protocol synopsis for such a study was submitted and is under consultative review by DEPI. With respect to hepatic adverse events, the Sponsor agreed to conduct enhanced pharmacovigilance. Finally, the Sponsor also agreed to revise the label and dose regimen so that mirabegron 25 mg is the starting dose, with allowance to increase dose to 50 mg in non-responders to 25 mg.

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/s/

A R WIEDERHORN
06/01/2012

MARK S HIRSCH
06/01/2012
I concur.

Medical Officer's Consultative Review of NDA 202-611
Ophthalmology

Submission date: August 30, 2011
Review date: May 4, 2012

Sponsor: Astellas Pharma

Product: Mirabegron

Pharmacologic Class: Selective beta 3-adrenoreceptor agonist

Proposed Indication: Treatment of overactive bladder

Requested: This new NDA 20211 was received on August 29, 2011, and it is fully electronic in EDR at: \\CDSESUB5\EVSPROD\NDA202611\0000. The related IND is 69,416. The PDUFA Goal Date is June 29, 2011.

Mirabegron is a beta-3 adrenergic agonist which has been developed for the treatment of overactive bladder. It is a new molecular entity, and to our knowledge, no currently approved product has this mechanism of action. Several adverse events of glaucoma were reported during the Phase 3 development program for mirabegron, and this prompted extensive discussions between sponsor and FDA, including consultation with Dr. Chambers in the Division of Transplant and Ophthalmologic Products. In order to address the Agency's concerns regarding glaucoma, Astellas conducted a systematic evaluation of glaucoma-type AE in all completed clinical studies 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 treatment-emergent adverse event (TEAE) in the glaucoma standardized MedDRA query (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 non-glaucoma, ocular hypertension (ocular hypertension, by definition, is not glaucoma):
- 1 patient with ocular hypertension

6 patients were classified as not having a treatment emergent adverse event 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. Following meetings with the Division and after consultation with DTOP, the sponsor agreed to conduct a randomized, double-blind, placebo-controlled, non-inferiority study to assess the effect of mirabegron on IOP. The study used a suprathreshold dose of mirabegron (100 mg) administered orally once daily for 8 weeks in healthy research subjects on intra-ocular pressure (IOP). The study results, in the sponsor's opinion, were that 100 mg of mirabegron administered once daily was non-inferior to placebo for the primary endpoint of change from baseline to day 56 in subject average IOP, based on the non-inferiority limit of 1.5 mm Hg. The sponsor concluded that these results and additional eye assessments in other phase 1 studies, as well as the program-wide evaluation of reported ocular events do not suggest an association of mirabegron and glaucoma or other ocular safety issues.

Questions for DTOP

1. Was the non-inferiority study conducted in accordance with DTOP recommendations?
2. Does DTOP agree with the interpretation of the study result by the Sponsor?
3. Does DTOP agree that mirabegron is not associated with increased IOP as evaluated in the study?
4. Does DTOP agree with the sponsor's conclusion that the available data does not suggest an association of mirabegron and glaucoma?
5. Does DTOP have any further recommendations in regard to mirabegron and glaucoma?
6. Are any other ocular safety issues noted by DTOP?

Clinical Study for Ocular Safety

A Phase 1b, Randomized, Double-Masked, Parallel Group, Placebo Controlled Study to Assess Intraocular Pressure and Ocular Safety of the Beta-3 Agonist Mirabegron in Research Subjects

Study Design: This was a double-masked, randomized, parallel group, placebo-controlled, phase 1b study. Approximately 320 subjects were planned for randomization to target 240 subjects to complete the study. Subjects were consented and screened to confirm inclusion/exclusion criteria including normal (≥ 10 mm Hg and ≤ 21 mm Hg) single-eye IOP in each eye.

The study consisted of 4 visits:

- Visit 1: screening (day -28 to day -4)
- Visit 2: baseline (day 1)
- Visit 3: day 10 (+ 2 days)
- Visit 4: day 56/end of treatment (EOT) (+ 3 days)

Each subject was randomized on a 1:1 basis to mirabegron or matching placebo and participated in a 56-day treatment period during which once daily dosing of mirabegron 100 mg or placebo occurred. This dose is 2-4 times the dose recommended for the treatment of hyperactive bladder.

Subjects were admitted to the study center the night prior to visits at baseline, day 10 and day 56. Subjects reported to the clinical research unit prior to 7 PM on the day before study visit 2 baseline day 1, visit 3 day 10 and visit 4 day 56/EOT. Subjects remained confined to the clinic until all study procedures were completed for each visit.

IOP was measured in both eyes using a Goldmann applanation tonometer at screening, baseline and at treatment days 10 and 56. At each site, all IOP measurements for each subject were performed by the same board-certified ophthalmologist using the same Goldmann applanation tonometer throughout the study. The Goldmann applanation tonometer was fully calibrated for accuracy within 1 month prior to screening the first subject and monthly during the conduct of the study. The fluorescein and anesthetic agents used for the tonometry were to be documented and were to remain consistent throughout the study.

IOP was to be measured in duplicate in each eye between the hours of 9 AM and 11 AM at each study visit. A third IOP measurement was to be taken if the difference between the first and second IOP measurement was ≥ 2 mm Hg for an eye.

The primary variable for determination of non-inferiority of mirabegron 100 mg once daily to placebo was the change from baseline to day 56 in subject-average IOP.

Schedule of Assessments for Ophthalmic Procedures

Assessments	Screening †	Study Visit			
	Day -28 to Day -4	Baseline Day 1	Day 10 (+ 2 days)	Day 56/EOT ‡, (± 3 days)	
	Visit 1	Visit 2	Visit 3	Visit 4	
Visual Acuity (ETDRS Method) §	X	X	X	X	
Automated Static Visual fields §	X				
Biomicroscopy ¶, ††	X	X	X	X	
Intraocular Pressure ¶, ‡‡	X	X	X	X	
Pachymetry §	X				
Ophthalmoscopy (dilated) ¶, §§	X				

ETDRS: early treatment of diabetic retinopathy study, charts for visual acuity; EOT: end of treatment; IOP: intraocular pressure.

† Screening procedures could either be performed all in one visit or may have been split and completed in multiple visits.

‡ Day 56/EOT procedures were to be completed for all subjects early terminating from the study. It is preferable to have the subject in overnight confinement prior to study visit and the IOP must still be completed within the 9 AM to 11 AM window.

§ A licensed ophthalmologist, optometrist or a certified ophthalmic assistant/technician was to perform this evaluation.

¶ A licensed ophthalmologist was to perform this evaluation. A nurse or certified ophthalmic assistant/technician may have administered the fluorescein, anesthetic or dilating agents as appropriate.

†† Included documentation of iris pigmentation color at screening.

‡‡ IOP was measured in duplicate in each eye between the hours of 9 AM and 11 AM at each study visit by the same ophthalmology reader using the same Goldmann applanation tonometer for each study subject.

Approximately 320 subjects were planned to target 240 subjects (120 subjects per treatment group) to complete 56 days of study drug, allowing for a 25% dropout rate. Based on standard deviation of subject-average IOP of 3.0 mm Hg, a 1-sided significant level of 0.025, an expected true difference between the 2 treatment groups of 0 mm Hg, 120 subjects per treatment group would provide 97% power to demonstrate non-inferiority. Non-inferiority was to be accepted if the upper limit of 2-sided 95% CI for the difference in mean change from baseline to day 56 in subject-average IOP between mirabegron and placebo was less than the non-inferiority margin of 1.5 mm Hg.

In a 2-treatment equivalency study of 332 glaucoma patients, [Mundorf et al, 2004] indicated standard deviations of unadjusted IOP from 2.6 to 3.2 mm Hg at various time points, and standard deviations for change from baseline from 2.6 to 3.0 mm Hg at various time points. Subjects in this current study were to be within the range of 10 to 21 mm Hg at baseline, and few subjects were expected to have IOPs ≥ 17 mm Hg. Based on this information, it could be expected that the standard deviation of the baseline IOP would be 3.0 mm Hg or less. Values for standard deviation for change from baseline in IOP between 2.5 and 3.0 mm Hg were plausible, assuming that baseline IOP and day 56 subject-average IOP were moderately correlated. Calculation of sample size was performed using nQuery Advisor version 6.01.

Reviewer's Comments: *The trial was appropriately designed to address the question of whether or not mirabegron causes an increase in intraocular pressure.*

Demographic and Other Baseline Characteristics

Parameter	Study Treatment		
	Placebo n = 159	Mirabegron 100 mg n = 161	Total n = 320
Gender			
Male	87 (54.7%)	91 (56.5%)	178 (55.6%)
Female	72 (45.3%)	70 (43.5%)	142 (44.4%)
Ethnicity			
Hispanic or Latino	66 (41.5%)	74 (46.0%)	140 (43.8%)
Not Hispanic or Latino	93 (58.5%)	87 (54.0%)	180 (56.3%)
Race			
White	145 (91.2%)	148 (91.9%)	293 (91.6%)
Black or African American	8 (5.0%)	10 (6.2%)	18 (5.6%)
Asian	3 (1.9%)	0	3 (0.9%)
American Indian or Alaska Native	3 (1.9%)	2 (1.2%)	5 (1.6%)
Naive Hawaiian or Other Pacific Islander	0	1 (0.6%)	1 (0.3%)
Age (Years)			
Mean (SD)	35.7 (12.14)	34.4 (11.02)	35.0 (11.59)
Median	34.0	33.0	34.0
Min – Max	19 - 75	18 - 70	18 - 75
Age Group (Years)			
18-24	33 (20.8%)	37 (23.0%)	70 (21.9%)
25-34	52 (32.7%)	48 (29.8%)	100 (31.3%)
35-44	40 (25.2%)	43 (26.7%)	83 (25.9%)
45-54	23 (14.5%)	26 (16.1%)	49 (15.3%)
55-64	6 (3.8%)	5 (3.1%)	11 (3.4%)
≥ 65	5 (3.1%)	2 (1.2%)	7 (2.2%)
Iris pigmentation color			
Blue	36 (23%)	30 (19%)	66 (21%)
Brown	87 (55%)	99 (62%)	186 (58%)
Green	12 (7%)	13 (8%)	25 (8%)
Grey	1 (1%)	0	1 (1%)
Hazel	23 (15%)	19 (12%)	42 (13%)
Central corneal thickness (microns) †			
Mean (SD)	547 (25)	550 (26)	548 (26)
Median	547	549	548
Min - Max	500 - 600	501 - 600	500 - 600
Mean deviation from static visual fields (dB) †			
Mean (SD)	-0.6 (1.2)	-0.7 (1.4)	-0.6 (1.3)
Median	-0.46	-0.45	-0.46
Min - Max	-7.7 – 2.1	-12.9 - 1.5	-12.9 - 2.1
Subject-average intraocular pressure (mm Hg) †			
Mean (SD)	15.4 (2.0)	15.3 (2.0)	15.4 (2.0)
Median	15.5	15.5	15.5
Min - Max	10.3 - 20.5	10.3 – 20.3	10.3 - 20.5
Visual acuity (logMAR) †			
Mean (SD)	-0.086 (0.078)	-0.082 (0.084)	-0.084 (0.081)
Median	-0.09	-0.08	-0.08
Min - Max	-0.24 - 0.15	-0.29 - 0.17	-0.29 - 0.17

Reviewer's Comments: *The population was balanced between groups.*

Change from Baseline in Subject-Average Intraocular Pressure (mm Hg)

Day 10

Statistic	Study Treatment	
	Placebo n = 158	Mirabegron 100 mg n = 159
Baseline, mean (SE)	15.4 (0.16)	15.3 (0.16)
Day 10, mean (SE)	15.1 (0.18)	15.0 (0.15)
Mean change from baseline (SE)	-0.3 (0.13)	-0.3 (0.11)
Adjusted mean (SE) change from baseline	-0.3 (0.11)	-0.3 (0.11)
95% 2-sided CI for adjusted change	(-0.5, -0.1)	(-0.5, -0.1)
Mean (SE) difference vs. placebo		0.0 (0.16)
95% 2-sided CI for difference		(-0.3, 0.3)

Day 56

	Placebo n = 156	Mirabegron 100 mg n = 154
Baseline, mean (SE)	15.4 (0.16)	15.3 (0.16)
Day 56, mean (SE)	15.2 (0.17)	15.0 (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)
95% 2-sided CI for adjusted change	(-0.4, 0.0)	(-0.5, -0.0)
Mean (SE) difference vs. placebo		-0.1 (0.17)
95% 2-sided CI for difference		(-0.4, 0.3)
Achieve non-inferiority criteria (yes or no)?		yes

All subjects who received study drug, provided a baseline and post-baseline 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.

ANCOVA: analysis of covariance; IOP: intraocular pressure

Reviewer's Comments: *The 95% confidence interval is well within the ± 1 mmHg limit, and therefore mirabegron is considered to be equivalent to placebo in its likelihood of raising intraocular pressure.*

Visual Acuity

Number and Percent of Subjects with Losses from Baseline in Visual Acuity at Any Visit

Parameter	Study	
	Placebo n = 159	Mirabegron 100 mg n = 161
≥ 0.1 logMAR worsening from baseline	47/159 (29.6%)	44/160 (27.5%)
≥ 0.2 logMAR worsening from baseline	5/159 (3.1%)	4/160 (2.5%)
≥ 0.3 logMAR worsening from baseline	1/159 (0.6%)	1/160 (0.6%)

All subjects who received at least 1 dose of study drug (Safety Analysis Set [SAF]).

Decrease in visual acuity for the worse eye was defined as loss of visual acuity from baseline in the eye with the greater loss.

Reviewer's Comments: *There were no significant differences between groups.*

Biomicroscopy of the Anterior Segment

Reviewer's Comments: *There were no significant anterior segment findings in either group.*

Responses to Questions

1. Was the non-inferiority study conducted in accordance with DTOP recommendations?

Reviewer's Response: *Yes.*

2. Does DTOP agree with the interpretation of the study result by the Sponsor?

Reviewer's Response: *Yes. Mirabegron in doses up to 100 mg daily does not appear to raise intraocular pressure.*

3. Does DTOP agree that mirabegron is not associated with increased IOP as evaluated in the study?

Reviewer's Response: *Yes.*

4. Does DTOP agree with the sponsor's conclusion that the available data does not suggest an association of mirabegron and glaucoma?

Reviewer's Response: *Yes.*

5. Does DTOP have any further recommendations in regard to mirabegron and glaucoma?

Reviewer's Response: *No further recommendations at this time.*

6. Are any other ocular safety issues noted by DTOP?

Reviewer's Response: *No ocular safety issues have been noted.*

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
05/10/2012

NDA 202611/S000

Medical Officer's 45-Day Filing Memorandum

Application Letter Date: August 26, 2011
60-Day Filing Review Date: October 28, 2011
Mid-Cycle Review Date: January 31, 2012
Prescription Drug User Fee Act (PDUFA) Goal Date: June 29, 2012

Related Submissions: IND 69,416

Reviewers: A. Roger Wiederhorn, M.D.
Medical Officer
Division of Reproductive and Urologic Products (DRUP)

Mark S. Hirsch, M.D.
Medical Team Leader, DRUP

Product, route and dose: mirabegron, 25 and 50 mg extended release tablets

Indication: Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency

I. Summary

Objective:

This review assesses whether NDA 202611 is suitable for filing under 21 CFR 314.50, Content and format of an application, and 21 CFR 314.71, Procedures for submission of a new NDA. This document also serves as the basis for communicating to sponsor potential clinical review issues identified during this initial review period.

Conclusion:

Following a preliminary review of three Phase 3 studies of efficacy and safety and an overview review of the remainder of the studies (including 29 phase I studies, 6 supportive phase 2 studies, 1 supportive phase 3 study, and 1 long-term controlled comparator study), the draft label, and financial disclosures for investigators of the three pivotal phase 3 studies, NDA 202611 is fileable from a clinical perspective.

II. Background

Brief Regulatory History:

Mirabegron is an agonist for human beta 3-adrenoceptor (beta 3-AR) developed by Astellas Pharma. The Sponsor seeks an indication for the treatment of OAB. Mirabegron is a new chemical entity, first-in-class compound with a distinct mechanism of action compared with the current standard of care, primarily antimuscarinics, as pharmacotherapy for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency. The proposed dose is 50 mg of mirabegron once daily with or without food. In patients with severe renal impairment or

with moderate hepatic impairment the recommended dose of mirabegron is 25 mg orally with or without food. Mirabegron has been approved for marketing in Japan.

The Sponsor opened IND 69,416 on May 9, 2006. An End-of-Phase 2 meeting was held with the Sponsor on November 14, 2007. At that time, the planned Phase 3 studies were discussed. Several safety issues were discussed, including elevations in liver function tests, and increases in blood pressure in some individuals in Phase 2 studies. The Division asked that these two issues be monitored in the Phase 3 studies. In January 2008, following submission of phase 3 study protocols for special protocol assessment (SPA), the Division provided the Sponsor with Phase 3 protocol review comments which recommended that a 25 mg dose of mirabegron be evaluated and [REDACTED] (b) (4)

At the Pre-NDA meeting held on November 2, 2010, the Phase 3 study results were shown and discussed. As part of the planned NDA, the Sponsor proposed to systematically review several adverse events of interest to which the Division agreed. These adverse events of interest were:

- Cardiovascular events including increases in blood pressure, QT prolongation or its sequelae, and cardiac arrhythmias;
- Urinary tract events, including urinary retention/acute urinary retention, urinary tract infection, and urolithiasis;
- Hypersensitivity reactions;
- Lowering of the blood pressure, syncope, and hypotension;
- Seizures;
- Increases in serum liver function tests;
- Cases reported as “glaucoma” or “increased intraocular pressure”; and
- Single reports of a variety of neoplasms

III. Efficacy Data Analysis Sets

Analysis Sets Supporting the OAB indication

Analyses supporting the OAB indication use data from the placebo, 4 mg tolterodine, 25 mg 50 mg and 100 mg mirabegron treatment groups of Studies 178-CL-046, 178-CL-047, and 178-CL-074. These are designated as the primary efficacy studies by the Sponsor.

An additional efficacy study, 178-CL-048, conducted in Japan, is also submitted.

Two supportive phase 2 studies (178-CL-045 and 178-CL-044) and 1 phase 2a proof-of-concept study (178-CL-044) are also submitted.

Data from the 12 month blinded study, 178-CL-049 comprise the primary long-term exposure analysis set as it relates to “persistence of effect”. In this double-blinded, active-controlled study, subjects previously assigned to placebo, 4 mg tolterodine, 25 mg, 50 mg and 100 mg mirabegron in the double-blinded 12 week studies were administered mirabegron 50 or 100mg or 4 mg tolterodine. Subjects naïve to mirabegron were also allowed to enroll.

A 52-week, open-label study conducted in Japan, 178-CL-051, utilized mirabegron 50 mg with dose escalation to 100 mg after 8 weeks.

IV. Safety Data Analysis Sets

The primary safety analysis set contains integrated data from the 12-week, double-blind, placebo controlled Pivotal Studies 178-CL-046, 178-CL-047 and 178-CL-074. Long term safety data is presented in the 1 year blinded and active-controlled Study 178-CL-049. Additional 1-year safety data is presented in the open-label Japanese Study 178-CL-051. Additional safety data is presented in integrated form from studies 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, and 178-CL-060.

V. NDA Filing Review

Filing Review: The review is based on three criteria proposed in FDA guidance for the filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50.

1. Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner.
2. Failure to include evidence of effectiveness compatible with the statute and regulations.
3. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Submitted materials:

The Sponsor submitted data from three phase 3 efficacy and safety studies (178-CL-046, 178-CL-047 and 178-CL-074). The global phase 2/3 population included the following studies: 178-CL-046, 178-CL-047, 178-CL-074, 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, and 178-CL-060. The Sponsor submitted data from 6 biopharmaceutical studies, 17 human pharmacokinetic studies and 5 human pharmacodynamic studies. These are summarized in the table below:

Table 1: Summary of Clinical Studies with Mirabegron included in Submission

Study Identifier	Study Objective	Design and Control Type	Test Product Dose Regimen Administration Route	Subject Number and Type	Duration of Treatment
Efficacy and Safety Studies					
178-CL-044 In 14 European Countries	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging	Treatment groups: placebo, mirabegron 25, 50, 100 or 200 mg, or tolterodine SR 4 mg or matching placebo po; once daily fed (after breakfast)	928 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-045 In Japan	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2, randomized, double-blind, placebo-controlled, parallel group	mirabegron 25, 50, or 100 mg qd or matching placebo tablet po; once daily fed (after breakfast)	842 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-046 in Europe and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg, or matching placebo po; once daily with or without food	1987 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period

178-CL-047 in Canada, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg or matching placebo po; once daily with or without food	1329 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-048 in Japan	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo- and active-controlled	Treatment groups: placebo, mirabegron 50 mg, or tolterodine SR 4 mg or matching placebo po; once daily with food (after breakfast)	1139 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double-blind treatment period

178-CL-049	Long Term Safety	Phase 3, randomized, double-blind, active-controlled	Treatment Groups: Mirabegron 50 or 100 mg or tolterodine ER 4 mg	2452	12 month double-blind treatment period
178-CL-074 in Canada, Europe and United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg or matching placebo po; once daily with or without food	1306 Adults with OAB	2-week single-blind placebo run-in followed by 12-week double blind treatment period
178-CL-008 in Europe	Efficacy, safety, tolerability, population PK; proof of concept	Phase 2a, randomized, double-blind, parallel group, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron IR 100 or 150 mg bid, or tolterodine MR 4 mg	262 Adults with OAB	2-week single-blind placebo run-in followed by 4-week double-blind treatment period
178-CL-060 in Canada and United States	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast	200 men with LUTS and BOO	12-week DB treatment period

178-CL-003 in Poland	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast	59 Adults with type 2 diabetes	4-week single-blind placebo run-in followed by 12-week double-blind treatment period: Mirabegron 60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks
178-CL-004 In Poland	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast Metformin 500 and 850 mg tablets po; stable dose throughout treatment period	60 Adults with type 2 diabetes on metformin monotherapy (stable doses)	4-week single-blind placebo run-in followed by 12-week double blind treatment period: Mirabegron 60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks
Biopharmaceutic Studies					
178-CL-033 in Netherlands	Absolute BA (iv vs OCAS tablet)	Phase 1, open label, randomized, 2-way crossover	Mirabegron OCAS 50 mg or 150 mg tablet po, 15 or 50 mg iv over 2 hours; fasted	12 Healthy Volunteers	Single Dose
178-CL-030 in Netherlands	PK, 3 OCAS formulations vs IR	Phase 1, open label, 3-way crossover	Mirabegron OCAS-F 200 mg qd (fed and fasted), OCAS-S 200 mg qd (fed and fasted), OCAS-M 200 mg qd (fed and	36 Healthy Volunteers	8 days each treatment (OCAS fasted, OCAS fed, IR fasted), washout of ≥7-days

			fasted); tablet po Mirabegron IR 100 mg bid (fasted); tablet po		between treatments
178-CL-041 in United States	Effect of food on PK of mirabegron	Phase 1, randomized open-label, 3-way crossover	Mirabegron OCAS 50 or 100 mg tablet po; single dose administered fasted, with high-fat breakfast or with low-fat breakfast	76 Healthy Volunteers	Single dose on day 1 of each of 3 periods; washout of ≥ 10 days between periods
178-CL-064 in Japan	Effect of food on PK of mirabegron	Phase 1 randomized, open label, 2-way crossover	Mirabegron OCAS 50 mg tablet po; single dose administered fasted or with high-fat breakfast	24 Health Male Volunteers	Single dose on day 1 of each of 2 periods; washout of ≥ 12 days between periods
178-CL-078 in Japan	Effect of food on PK of mirabegron	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	Mirabegron iv 7.5, 15 or 30 mg iv over 120 minutes and mirabegron OCAS 25, 50 mg or 100 mg tablet po (fast-release, target-release, slow-release and other target release); fasted	72 Healthy Volunteers	Single dose on day 1 of each of 3 periods; washout of ≥ 12 days between treatments
178-CL-076 In United States	PK, iv and 3 OCAS formulations	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	Phase 1, open label, 5-way crossover, with 3 of the treatments given in random order	91 Healthy Volunteers	Single dose on day 1 of each of 5 periods; washout of ≥ 10 days between treatments
Human Pharmacokinetic Studies					
178-CL-001 in United Kingdom	PK, safety, tolerability, food	Part I Phase 1, placebo	Placebo or mirabegron IR 0.1, 0.3, 1, 3, 10, 30,	85 Healthy Male Volunteers	Single dose

	effect	controlled, randomized, double-blind, dose escalation study	100, 160, 240, or 340 mg po; fasted		
		Part II Phase 1, open-label, randomized, 3-way crossover	Mirabegron IR 160 mg capsule (two 80 mg capsules) po; fed (with high-fat breakfast), semi-fed (30 min before high-fat breakfast), and fasted	12 Healthy Male Volunteers	Single dose, 7 day washout between doses
178-CL-002 in United Kingdom	PK, safety, tolerability, PD	Phase 1, placebo controlled, Double blind, randomized, dose-escalation study	Mirabegron IR 40, 80, 160, 240 mg capsule (20 and 80 mg capsules) po; once daily fasted Mirabegron IR 240 mg capsule (80 mg capsules) po; once daily fed (high-fat breakfast days 1 and 9; standard breakfast days 2-8)	40 Healthy Male Volunteers	Single dose on day 1 followed by once daily dosing for 7 days (days 3-9)
178-CL-007 in Netherlands	PK/mass balance	Phase 1, open-label study	C ¹⁴ -mirabegron 160 mg drinking solution; fasted	4 Healthy Male Volunteers	Single Dose
178-CL-031 in Netherlands	PK, safety, tolerability of OCAS-M formulation, explore PK in elderly and young	Phase 1, double blind, randomized, placebo-controlled, dose-escalating study	Mirabegron OCAS-M 50, 100, 200, 300 mg po; fasted on PK days, otherwise standard breakfast was served	96 healthy Volunteers	Single dose OCASM on day 2 followed by qd dosing for 10 days (days 5-14)
178-CL-066 in Japan	Dose proportionality	Phase 1 open-label,	Mirabegron OCAS 25, 50,	12 Healthy non-elderly	Single dose on

	of mirabegron	3-period, dose escalation	and 100 mg tablet po; fasted	male volunteers	day 1 of each of 3 periods; washout of ≥ 12 days between treatments
178-CL-034 in Japan: Single Dose	PK of mirabegron after single and repeated dosing	Phase 1, single blind, Placebo controlled, singled dose and repeated dose study	Single dose: Mirabegron OCAS 0 (placebo), 50, 100, 200, 300, or 400 mg; tablets po; fasted	40 Healthy Male Volunteers	Single Dose
178-CL-034 in Japan: Repeat Dose			Repeated dose: Mirabegron OCAS 0 (placebo), 100, or 200 mg tablet po; 30 min to 1 hour after breakfast	24 Healthy Male Volunteers	Single dose followed by 2-day washout, followed by 7 days
178-CL-072 in France	PK, safety, tolerability, age and gender effects	Phase 1, open-label, randomized, 2-way crossover	Mirabegron OCAS 25, 50 and 100 mg tablet po; 30 minutes after breakfast and dinner on day 1, 30 minutes after breakfast on days 2-5, fasted on days 6 and 7	75 Healthy Volunteers	Two 7-day treatment periods; morning and evening dose on day 1, single morning doses on days 2-7; washout of ≥ 14 days between treatments Treatment sequences included (Period 1 to Period 2): 25 to 50 mg; 50 to 25 mg, 25 to 100 mg; 100 to 25 mg; 50 to 100 mg; 100 to 50 mg

178-CL-038 in United States	PK, safety, tolerability, renal impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	33 Healthy Volunteers with mild to severe renal impairment	Single dose
178-CL-039 in Slovakia	PK, safety, tolerability, hepatic impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	32 Healthy Volunteers with mild or moderate hepatic impairment	Single dose
178-CL-005 In Netherlands	Part 1: PK in poor and extensive CYP2D6 metabolizers	Phase 1, open-label, 1-sequence, parallel study	Mirabegron IR 160 mg capsules (two 80 mg capsules) po; fasted	16 Healthy male volunteers (extensive and poor CYP2D6 metabolizers)	Single dose
	Part 2: DDI of mirabegron and metoprolol (CYP2D6 substrate)	Phase 1, open-label, cross-over	Mirabegron IR 160 mg capsules (two 80 mg capsules) once daily po; fasted metoprolol tartrate 100 mg tablet; fasted	12 Healthy male volunteers (extensive CYP2D6 Metabolizers)	7 days total single dose metoprolol on days 1 and 7, mirabegron on days 3-7
178-CL-006 in Netherlands	DDI of mirabegron and metformin	Phase 1, one sequence crossover	Mirabegron IR 160 mg tablets (one 100 mg tablet and two 30 mg tablets) po; once daily fasted Seq A: metformin 500 mg tablets; twice daily on days 12-15, single morning dose on day 16, fasted (morning dose only) Seq B: metformin 500 mg tablets; twice daily on days 1-4 and 6-15, single morning	32 Healthy Male Volunteers	Sequence A: mirabegron days 1-11 and mirabegron+metformin or placebo days 12-16 Sequence B: metformin days 1-5 and metformin +mirabegron or placebo days 6-16

			dose on day 5 and 16, fasted (morning dose only)		
178-CL-058 in France	Effect of steady state mirabegron on PK of single dose desipramine	Phase 1, open-label, 1-sequence crossover study	Mirabegron OCAS 100 mg tablet po, only daily fasted; Desipramine 50 mg tablets (as two 25 mg tablets) po, fasted	28 Healthy volunteers	Period 1: desipramine 50 mg single dose on day 1; mirabegron 100 mg qd (day 5 to 23); desipramine 50 mg single dose in combination with mirabegron on day 18 (washout period 13 days) Period 2: desipramine 50 mg single dose on day 38
178-CL-068 in France	Effect of multiple doses of mirabegron on the PK of a COC	Phase 1, double-blind, 2-sequence crossover study	Mirabegron OCAS 100 mg or matching placebo tablet po; once daily fasted Combined oral contraceptive (COC) (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) tablet po; once daily fasted	30 Healthy Female Volunteers	Dosed according to menstrual cycle Period 1: COC qd day 1 to day 21; stop for 7 days; start mirabegron 100 mg or matching placebo qd day 12 for 10 days (washout period 19 days) Period 2: COC qd

					day 1 to day 21; start mirabegron 100 mg or matching placebo qd (opposite of period 1) day 12 for 10 days
178-CL-059 in France	Effect of steady state mirabegron on PK of single dose digoxin	Phase 1, open-label, 1-sequence crossover study	Mirabegron OCAS 100 mg tablet po, only daily fasted; Digoxin 0.250 mg tablet po; fasted	25 Healthy volunteers	Digoxin 0.250 mg single dose on day 1; mirabegron 100 mg qd (day 10 to day 23); digoxin 0.250 mg single dose in combination with mirabegron dose on day 18
178-CL-040 in France	Effect of mirabegron at steady state on the PK of single dose of warfarin	Phase 1, open-label, 1-sequence crossover	Mirabegron OCAS 100 mg po; once daily fasted Warfarin 25 mg tablet (as five 5 mg tablets) po; once daily fasted	24 Healthy volunteers	Warfarin 25 mg single dose on day 1 washout period of 14 days mirabegron 100 mg qd for 16 consecutive days (day 15 to day 30) warfarin 25 mg single dose on day 23
178-CL-069	Effect of	Phase 1,	Mirabegron OCAS	41 Healthy	Treatment

in France	steady state mirabegron on PK of single dose solifenacin and effect of steady state solifenacin on PK of single dose mirabegron	open-label, 1-sequence, 2-arm study	100 mg tablet po, once daily fasted Solifenacin 10 mg tablet po; once daily fasted	Volunteers	arm 1: solifenacin 10 mg single dose day 1 (washout 14 days); mirabegron 100 mg qd day 15 to 38; solifenacin 10 mg single dose in combination with mirabegron dose on day 23 Treatment arm 2: mirabegron 100 mg single dose day 1 (washout 6 days); solifenacin 10 mg qd day 7 to 20; mirabegron 100 mg single dose in combination with solifenacin dose on day 16
178-CL-080 in France	Cardiovascular interactions between mirabegron and tamsulosin	Phase 1, open-label, 2-arm, 2-sequence crossover	Mirabegron OCAS 100 mg po; once daily fasted Tamsulosin 0.4 mg capsule po; once daily fasted	48 Healthy Volunteers	Arm 1, Sequence 1: tamsulosin 0.4 mg on day 2 (washout 22 days), mirabegron 100 mg days 27 to 39, tamsulosin

					<p>0.4 mg single dose on day 35</p> <p>Arm 1, Sequence 2: mirabegron 100 mg days 2-14, tamsulosin 0.4 mg single dose on day 10 (washout 10 days); tamsulosin 0.4 mg single dose on day 27</p> <p>Arm 2, Sequence 1: mirabegron 100 mg on day 2 (washout 18 days) tamsulosin 0.4 mg days 23-35, mirabegron 100 mg single dose on day 27</p> <p>Arm 2, Sequence 2: tamsulosin 0.4 mg days 2-14, mirabegron 100 mg single dose on day 6 (washout 6 days); mirabegron 100 single dose on day 23</p>
Human Pharmacodynamic Studies					
178-CL-037	Thorough QT	Phase 1,	Mirabegron OCAS	49 Healthy	Four 7-day

in United States		randomized, double-blind, placebo- and active-controlled, 4-way crossover	100 and 200 mg tablet; moxifloxacin 400 mg capsule; matching placebo tablet (mirabegron) and capsule (moxifloxacin) po; once daily fasted	Volunteers	treatment periods; washout of ≥ 10 days between treatments Mirabegron/ matching placebo: 7 days Moxifloxacin: placebo to match mirabegron days 1-6, moxifloxacin/ matching placebo on day 7
178-CL-077 in United States	Thorough QT	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group, 2-way crossover	Mirabegron OCAS 50, 100 or 200 mg tablet or moxifloxacin 400 mg capsule po; and matching placebo; once daily fasted	352 Healthy Volunteers	Two 10-day treatment periods; washout of ≥ 10 days between treatments
178-CL-053 in France	Cardiovascular mechanistic study	Phase 1, randomized, single blind, 2-arm, 3-way crossover design	Mirabegron OCAS 200 mg tablets (2x 100 mg) po; matching placebo; fasted Propranolol 160 mg capsule (prolonged release) po, Bisoprolol 10 mg tablet po ; or matching placebo; fasted	12 Healthy Male Volunteers	Day 1: Propranolol, bisoprolol or placebo followed by mirabegron placebo; Day 5: Propranolol, bisoprolol or placebo followed by mirabegron 200 mg; minimum of 14 days between each dose of mirabegron

178-CL-081 in United States	Ocular Safety	Phase 1b, randomized, double-masked, 2-arm, parallel group	Mirabegron OCAS 100 mg tablets po; matching placebo; once daily fasted	321 Research subjects (Healthy volunteers or adults with overactive bladder)	56 days
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Source: Table 1, Listing of Clinical Studies, CTD module 5.2, page 2

In the pivotal and additional analysis sets supporting the OAB indication, mirabegron was studied in a total 4285 patients with OAB in six 12-week efficacy studies. The phase 3 program evaluated doses of 25, 50 or 100 mg of mirabegron once daily.

Table 2: Patients Treated in the Phase 2/3 Clinical Population

Study	Treatments							
OAB 12-Week Phase 2/3 Population								
	Placebo	Total Daily Dose of Mirabegron				Total Mirabegron	Tolterodine ER 4mg	
		25mg	50mg	100mg	200mg			
178-CL-046	494		493	496		989	495	
178-CL-047	453		442	433		875		
178-CL-074	433	432	440			872		
Phase 3 Total 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 in the Phase 2/3 Population								
	Placebo	25mg	50mg	100mg	200mg	300mg	Total	Tolterodine ER 4mg
178-CL-003	19				40		40	
178-CL-004	20				40		40	
178-CL-008	66				65	65	130	64
178-CL-060	65		70	65			135	
Totals	170		70	65	145	65	345	64

Source: Table 4, Summary of Clinical Safety, current submission, page 23

Table 3: Long Term Controlled Population

Study	Mirabegron mg/day		New Exposure	Re-Exposure	Tolterodine ER 4 mg
	50mg	100mg			
178-CL-049	812	820	901	731	812
Total Mirabegron Exposure =1632					
Japan Long-Term Uncontrolled Population					
178-CL-051	50 mg (only)	100 mg (used)			
	153	50			
Total Mirabegron Exposure=203					

Source: Table 4, Summary of Clinical Safety, current submission, page 23

The Sponsor states the total number of unique mirabegron patients in the Global Phase 2/3 Population is 4414+345+901+203=5865.

Question-Based Filing Review

1. Does this amendment omit a section required under CFR 314.50 or was a particular section presented in such a manner as to render it incomplete for the clinical review?

Response: No.

This NDA contains the critical sections in sufficient detail (see Table 2 and Appendix A).

Table 1: Checklist for Critical Sections

Comprehensive table of contents	Yes
Summary of the Application	Yes
Technical sections (CMC, Pharmacology/Toxicology, Clinical Pharmacology, Clinical)	Yes
Case Report Forms and Tabulations	Yes

- 1. Does the NDA(s) clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:**
- a) Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints.**
 - b) Presentation or what appears to be only a single adequate and well controlled study without adequate explanation.**
 - c) Use of a study design clearly inappropriate.**

VI. Preliminary Efficacy Findings

The following section of the filing review summarizes the preliminary efficacy findings from the randomized, double-blind, placebo controlled studies 178-CL-046, 178-CL-047 and 178-CL-074 and the 1 year controlled extension study 178-CL-049.

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

This Phase 3 multinational, multicenter study was conducted at 189 sites in 26 countries in Europe and Australia. A total of 200 sites were initiated; 189 sites enrolled patients.

The primary objective of the study was to assess the efficacy of mirabegron 50 mg once daily (qd) and mirabegron 100 mg qd against placebo in the treatment of patients with symptoms of overactive bladder (OAB). There were 2 secondary objectives:

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

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

2336 patients enrolled and 1987 patients were randomized as follows:

- Full Analysis Set: 1906 patients: placebo 480 patients; mirabegron 50 mg: 473 patients; mirabegron 100 mg: 478 patients; tolterodine SR 4 mg: 475 patients.
- Full Analysis Set Incontinence: 1165 patients: placebo 291 patients; mirabegron 50 mg: 293 patients; mirabegron 100 mg: 281 patients; tolterodine SR 4 mg: 300 patients.

Study Design

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

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

The co-primary efficacy variables included:

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

The key secondary efficacy variables included:

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

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

Safety variables included:

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

Statistical Methods

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

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

Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage described above.

Population

In the Safety population, overall, 72.2% of patients were female. The mean age was 60.0 years, with a range of 20 to 95 years of age. The majority (62.9%) of patients were < 65 years of age and 91.3% were < 75 years of age. Overall, 99.1% of patients were white. Mean body mass index across all treatment groups was 27.8 kg/m².

Efficacy results:

Table 5: Efficacy Results Study 178-CL-046

		Mirabegron		Tolterodine ER 4 mg
Co-Primary Efficacy Results		50 mg	100 mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr (FAS-I)				
n		293	281	300
Adjusted mean difference vs placebo(SE)		-0.41 (0.160) p=0.003	-0.29 (0.162) p=0.010	-0.10 (0.159) p=0.11
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)				
n		473	478	475
Adjusted mean difference vs placebo(SE)		-0.60(0.156) p=<0.001	-0.44(0.156) p=0.005	-0.25(0.156) p=0.11
Key Secondary Efficacy Results				
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)				
n		472	478	475
Adjusted mean difference vs placebo(SE)		11.9 (2.83) p=<0.001	13.2 (2.82) p=<0.001	12.6 (2.83) p=<0.001
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)				
n		293	281	299
Adjusted mean difference vs placebo(SE)		-0.39 (0.167) p=0.002	-0.38 (0.169) p=0.002	-0.35 (0.166) p=0.019
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)				
n		471	477	474
Adjusted mean difference vs placebo(SE)		-0.40 (0.136) p=0.004	-0.52 (0.136) p=<0.001	-0.33 (0.136) p=0.016

Source: Table 1, Summary of Clinical Efficacy, current submission, page 9 For placebo results for co-primary endpoints, see the following 2 tables.

Table 6: Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Placebo (n=291)	Mirabegron		Tolterodine
		50 mg (n=293)	100 mg (n=281)	SR 4 mg (n=300)
Baseline				
Mean (SE)	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)
Final Visit				
Mean (SE)	1.54 (0.145)	1.22 (0.133)	1.37 (0.134)	1.42 (0.145)
Change From Baseline				
Mean (SE)	-1.13 (0.126)	-1.62 (0.137)	-1.51 (0.115)	-1.21 (0.112)
p-Value		0.003	0.010	0.11
Statistically Superior to Placebo at the 0.05 Level with Multiplicity Adjustment		Yes	Yes	No

Source: Table 17, 178-CL-046 Study Report, page 99.

Table7: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo (n=480)	Mirabegron		Tolterodine
		50 mg (n=473)	100 mg (n=478)	SR 4 mg (n=475)
Baseline				
Mean (SE)	11.71 (0.143)	11.65 (0.137)	11.51 (0.124)	11.55 (0.128)
Final Visit				
Mean (SE)	10.35 (0.144)	9.70 (0.139)	9.76 (0.144)	9.97 (0.162)
Change From Baseline				
Mean (SE)	-1.37 (0.115)	-1.94 (0.116)	-1.75 (0.110)	-1.57 (0.123)
p-Value		<0.001	0.005	0.11
Statistically Superior to Placebo at the 0.05 Level with Multiplicity Adjustment		Yes	Yes	No

Source: Table 18, 178-CL-046 Study Report, page 100.

There was no significant treatment group by subgroup interaction for sex, age group (< 75, ≥ 75) and geographic region for the change from baseline to Final Visit in mean number of incontinence episode per 24 hours. The test for interaction by age < 65 versus age ≥ 65 revealed a p-value of 0.078, which the study report describes as “significant”. Table 20 of the study report appears to show better treatment effect in the older (≥ 65 years) population compared to the younger. Interaction by race could not be performed as 99% of subjects were white.

Reviewer’s Efficacy Conclusions: Upon preliminary review, the statistically significant efficacy of mirabegron (with correction for multiplicity) for the treatment of OAB has been demonstrated in Study 046. Mirabegron upon preliminary review has also demonstrated efficacy for the key secondary endpoints in this study. The difference in efficacy between older (≥ 65 years) and younger (< 65 years) patients observed in this study will be a review issue.

Study CL-178-047(ARIES): A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects with Symptoms of Overactive Bladder

This multinational, multicenter study was conducted at 132 sites in the United States (115 sites) and Canada (17 sites). A total of 141 sites were initiated; 132 sites enrolled patients.

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

This was a randomized, parallel group, placebo-controlled, double-blind, multinational, multicenter study conducted in patients with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) of at least 3 month’s duration. After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg

or a matching placebo qd for a 12-week, double-blind, placebo-controlled treatment period that consisted of visits at weeks 4, 8 and 12 and a 30-day follow-up telephone contact or visit.

2149 patients enrolled and 1329 patients were randomized as follows:

- Full analysis set: 1270 patients: Placebo: 433 patients; mirabegron 50 mg: 425 patients; mirabegron 100 mg: 412 patients
- Full Analysis Set Incontinence (FAS-I): 933 patients: Placebo: 325 patients; mirabegron 50 mg: 312 patients; mirabegron 100 mg: 296 patients
- Safety Analysis Set: 1328 patients: Placebo: 453 patients; mirabegron 50 mg: 442 patients; mirabegron 100 mg: 433 patients

Study Design: The inclusion/exclusion criteria were the same across the 3 primary efficacy and safety studies, except in Study 178-CL-046, where criteria were added to accommodate precautions for use of tolterodine.

The co-primary efficacy variables included:

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

The key secondary efficacy variables included:

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

Safety variables included:

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

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

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

Since 2 mirabegron treatment groups were compared with placebo, the Hochberg procedure was performed at the alpha = 0.05 level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the alpha=0.25 level.

The planned analyses were changed as five patients were enrolled into the study on 2 separate occasions; in each case, this occurred at 2 different study sites. Of these, 4 patients were randomized twice and therefore analyzed as 8 unique patients. All preplanned efficacy and safety analyses were conducted with these patients included as 8 unique patients. Additional sensitivity analyses, excluding the 8 patient numbers assigned to these 4 patients, were conducted for the co-primary and key secondary efficacy variables.

Efficacy Results:

Table 8: Study 178-CL-047 Co-primary and Key Secondary Efficacy Results

Co-Primary Efficacy Results	Mirabegron		
	50 mg	100 mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr (FAS-I)			
n	312	296	
Adjusted mean difference vs placebo(SE)	-0.34(0.160) p=0.026	-0.50 (0.162) p=<0.001	
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
n	425	412	
Adjusted mean difference vs placebo(SE)	-0.61 (0.188) p=0.001	-0.70 (0.189) p=<0.001	
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
n	424	412	
Adjusted mean difference vs placebo(SE)	11.1 (3.43) p=0.001	11.0 (3.45) p=0.002	
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
n	309	293	
Adjusted mean difference vs placebo(SE)	-0.48 (0.166) p=0.003	-0.46 (0.168) p=<0.001	
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
n	422	409	
Adjusted mean difference vs placebo(SE)	-0.42 (0.182) p=0.022	-0.60 (0.183) p=0.001	

Source: Table 1, Summary of Clinical Efficacy, current submission, page 9. For placebo comparisons see the following two tables.

Table 9: Study CL-178-047 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo		Mirabegron	
		50 mg	100 mg	
	(n=433)	(n=425)	(n=412)	
Baseline				
Mean (SE)	11.51 (0.157)	11.80 (0.168)	11.66 (0.167)	
Final Visit				
Mean (SE)	10.51 (0.164)	10.09 (0.175)	9.91 (0.166)	
Change from Baseline				
Mean (SE)	-1.00 (0.140)	-1.71 (0.145)	-1.75 (0.135)	
p-Value		0.001	<0.001	
Statistically Superior to Placebo at the 0.05 Level With Correction for Multiplicity		Yes	Yes	

Source: Table 14, Study CL-178-047, page 97

Table 10: Study 178-CL-047 Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Placebo		Mirabegron	
		50 mg	100 mg	
	(n=325)	(n=312)	(n=296)	
Baseline				
Mean (SE)	3.03 (0.171)	2.77 (0.150)	2.69 (0.142)	
Final Visit				
Mean (SE)	1.81 (0.152)	1.33 (0.133)	1.14 (0.128)	
Change from Baseline				
Mean (SE)	-1.22 (0.152)	-1.44 (0.126)	-1.56 (0.130)	
p-Value		0.026	<0.001	
Statistically Superior to Placebo at the 0.05 Level With Correction for Multiplicity		Yes	Yes	

Source: Table 14, Study 178-CL-047, page 96

The co-primary efficacy variables were summarized using the FAS-I and the FAS for the following subgroups: sex, age group (< 65, ≥ 65 and < 75, ≥ 75), race and geographical region. Interpretation of the results of subgroup analyses is limited due to disproportionate numbers of patients in the subgroups for some variables and the influence of sample size on results. There was no significant treatment group by subgroup interaction for age group, race and geographical region for the change from baseline to Final Visit in mean number of incontinence episodes per 24 hours.

The treatment by sex interaction for incontinence episodes was significant (P=0.003). Among male patients, the adjusted mean difference versus placebo was 0.77 (95% CI: 0.03, 1.50) in the mirabegron 50 mg group and 0.42 (95% CI: -0.34, 1.18) in the mirabegron 100 mg group. Among female patients, the adjusted mean difference versus placebo was -0.59 (95% CI: -0.93, -0.24) in the mirabegron 50 mg group and -0.69 (95% CI: -1.04, -0.34) in the mirabegron 100 mg group.

Reviewer's Efficacy Conclusions: Upon preliminary review, the statistically significant efficacy of mirabegron (with correction for multiplicity) for the treatment of OAB has been demonstrated in Study 047. Mirabegron upon preliminary review has also demonstrated efficacy for the key secondary endpoints in this study.

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

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

This was a phase 3, randomized, parallel group, placebo-controlled, double-blind, multicenter, multinational study conducted in female and male patients of at least 18 years of age with symptoms of OAB syndrome (urinary frequency and urgency with or without incontinence) present for at least 3 months. After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline (visit 2), patients who met inclusion criteria and did not meet exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 25 mg, mirabegron 50 mg or a matching placebo once daily for a 12-week double-blind, placebo-controlled, treatment period that consisted of visits at weeks 4, 8 and 12 with a 2-week follow-up visit after end of treatment.

2201 patients were enrolled and 1306 patients were randomized as follows:

- Full Analysis Set: 1251 patients: placebo: 433 patients; mirabegron 25 mg: 433 patients; mirabegron 50 mg: 440 patients
- Full Analysis Set Incontinence: 773 patients: placebo: 262 patients; mirabegron 25 mg: 254 patients; mirabegron 50 mg: 257 patients
- Safety Analysis Set: 1305 patients: placebo: 433 patients; mirabegron 25 mg: 432 patients; mirabegron 50 mg: 440 patients

Study Design: The inclusion/exclusion criteria were the same across the primary studies, except in Study 178-CL-046, where criteria were added to accommodate precautions for the use of tolterodine.

The co-primary efficacy variables included:

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

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

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

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

Safety variables included:

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

Statistical Methods: Since there were 2 co-primary efficacy variables and 6 key secondary efficacy variables, the type I error rate was controlled at the $\alpha = 0.05$ level using a stepwise parallel gatekeeping procedure. At each of the 8 stages, the difference between a mirabegron dose group and placebo had to be statistically significant before a mirabegron dose group proceeded to the next stage. The stages and efficacy variables that were evaluated were as follows:

- Stage 1: incontinence episodes at final visit
- Stage 2: micturitions at final visit
- Stage 3: volume voided per micturition at final visit
- Stage 4: incontinence episodes at week 4
- Stage 5: micturitions at week 4
- Stage 6: level of urgency at final visit
- Stage 7: urgency incontinence episodes at final visit
- Stage 8: urgency episodes (grade 3 or 4) at final visit

Since 2 mirabegron groups were compared with placebo, the Hochberg procedure was performed at the $\alpha = 0.05$ level to adjust for multiplicity within each stage described above. If only 1 of the mirabegron dose groups proceeded to the next stage for any efficacy variable, then the comparison between mirabegron and placebo was assessed at the $\alpha = 0.025$ level.

Efficacy Results:

Table 11: Co-primary and Key Secondary Endpoints Study 178-CL-074

Co-Primary Efficacy Results	Mirabegron		
	25mg	50mg	
Change from Baseline to Final Visit in Mean Number of Incontinence per 24 hr (FAS-I)			
n	254	257	
Adjusted mean difference vs placebo(SE)	-0.40 (0.17) p=0.005	-0.42 (0.17) p=0.001	
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
n	410	426	
Adjusted mean difference vs placebo(SE)	-0.47 (0.18) p=0.007	-0.42 (0.17) p=<0.015	
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
n	410	426	
Adjusted mean difference vs placebo(SE)	4.6 (3.16) p=0.015	12.4 (3.13) p=<0.001	
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
n	254	255	
Adjusted mean difference vs placebo(SE)	-0.34 (0.17) p=0.039	-0.51 (0.17) p=<0.001	
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
n	410	424	
Adjusted mean difference vs placebo(SE)	-0.18 (0.176) p=0.30	-0.37 (0.17) p=0.035	

Source: Table 1, Summary of Clinical Efficacy, page 9. For placebo comparisons see the following 2 tables.

Table 12: Study 178-CL-074 Change from Baseline to Final in Mean Number of Incontinence Episodes per 24 hours

	Placebo	Mirabegron	
		25 mg	50 mg
	(n=262)	(n=254)	(n=257)
Baseline			
Mean (SE)	2.43 (0.145)	2.65 (0.160)	2.51 (0.146)
Final Visit			
Mean (SE)	1.54 (0.151)	1.21 (0.131)	1.13 (0.128)
Change from Baseline			
Mean (SE)	-0.89 (0.159)	-1.36 (0.145)	-1.38 (0.123)
p-Value		0.005	0.001
Superior to placebo at 0.05 level with multiplicity adjustment		Yes	Yes

Source: Table 17, 178-CL-074 Study Report, Page 105

Table 13: Study 178-CL-074 Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours

	Placebo	Mirabegron	
		25 mg	50 mg
	(n=415)	(n=410)	(n=426)
Baseline			
Mean (SE)	11.48 (0.142)	11.68 (0.153)	11.66 (0.156)
Final Visit			
Mean (SE)	10.33 (0.166)	10.02 (0.175)	9.33 (0.166)
Change from Baseline			
Mean (SE)	-1.15 (0.139)	-1.66 (0.145)	-1.62 (0.130)
p-Value		0.007	<0.015
Superior to placebo at 0.05 level with multiplicity adjustment		Yes	Yes

Source: Table 18, 178-CL-074 Study Report, page 106

The co-primary efficacy variables were summarized using the FAS and the FAS-I for the following subgroups: sex, age group (< 65, ≥ 65 and < 75, ≥ 75), race and geographical region. Only subgroups which had at least 10 patients in each treatment group were included in the estimation of the subgroup by treatment interaction. Interpretation by the Sponsor of the results of subgroup analyses is limited due to disproportionate numbers of patients in the subgroups for some variables and the influence of sample size on results. There was no statistically significant treatment group by subgroup interaction for sex (P=0.13), age group (P=0.41 for age cut off of 65 years and P=0.77 for the age cut off of 75 years), race (P=0.44) or geographical region (P=0.21) for the change from baseline to final visit in mean number of incontinence episodes per 24 hours. The treatment by sex interaction, while not significant, did reach the P-value < 0.15 (P=0.13) the threshold for further analysis. The findings for mean number of micturitions for 24 hours were similar.

Reviewer's Efficacy Conclusions: In Study 074, for both co-primary endpoints mirabegron 25 mg and 50 mg groups (with adjustments for multiplicity) were statistically superior to placebo. Mirabegron 50 mg had a statistically greater increase from baseline to final visit compared to placebo in the mean voided volume while mirabegron 25 mg did not. As a result, subsequent endpoints for mirabegron 50 mg were evaluated at the 0.025 significance level and subsequent endpoints for mirabegron 25 mg were excluded. Mirabegron 50 mg group had a statistically significant greater reduction from baseline to first measured time postdose at week 4 compared to placebo in the mean number of incontinence episodes per 24 hours. Due to the gatekeeping procedure, statistical significance was not achieved or any other secondary safety variables for either treatment group.

Table 14: Summary of Efficacy Results from Studies 046, 047 and 074: For Incontinence Episodes, Micturitions per 24 hours, Mean Voided Volume per Micturition.

	178-CL-046				178-CL-047			178-CL-074		
Incont/24 hours	P	M 50mg	M 100mg	T	P	M 50mg	M 100mg	P	M 25mg	M 50mg
n	291	293	281	300	325	312	296	262	254	257
Bsl	2.67	2.83	2.89	2.63	3.03	2.77	2.69	2.43	2.65	2.51
Final	1.54	1.22	1.37	1.42	1.81	1.33	1.14	1.54	1.21	1.13
Δ	-1.13	-1.62	-1.51	-1.21	-1.22	-1.44	-1.56	-0.89	-1.44	-1.37
p		0.003	0.010	0.11		0.26	<0.001		0.005	0.001
Mict/24 hours	Mean									
n	480	473	478	475	433	425	412	415	410	426
Bsl	11.71	11.65	11.51	11.55	11.51	11.80	11.66	11.48	11.68	11.66
Final	10.35	9.70	9.76	9.97	10.51	10.09	9.91	10.33	10.02	10.04
Δ	-1.37	-1.94	-1.75	-1.57	-1.00	-1.71	-1.75	-1.15	-1.66	-1.62
p		<0.001	0.005	0.11		0.001	<0.001		0.007	0.015
Voided Volume	Mean in mL									
Bsl	157.7	161.1	158.2	158.6	157.5	156.3	157.6	164.0	165.2	159.3
Final	169.1	185.2	183.8	183.6	164.6	174.4	175.4	172.3	176.6	183.3
Δ	12.4	24.1	25.6	25.0	7.1	18.1	17.8	8.3	12.5	21.1
p		<0.001	<0.001	<0.001		0.001	0.002		0.15*	<0.001*

P=placebo M=mirabegron T=tolterodine ER 4 mg Bsl = mean baseline Final=final Visit mean Δ= mean change from baseline Incont=incontinence episodes per 24 hr. p=p value, *=with multiplicity adjustment was not statistically significant.

Reviewer's Comment: The doses of 25, 50, or 100 mg mirabegron orally once daily evaluated in the primary efficacy studies [Studies 178-CL-046, 178-CL-047, and 178-CL-074] demonstrate the statistically significant efficacy of mirabegron 25, 50, and 100 mg compared with placebo for the co-primary endpoints of change from baseline to final visit in mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. The 25 mg dose demonstrates a smaller, non-statistically significant increase in volume voided, a key pharmacodynamic secondary endpoint.

Both mirabegron 50 and 100 mg demonstrated statistically significant 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.

Study 178-CL-049: A Randomized, Double-Blind, Double-Dummy, Parallel Group, Active Controlled, Multi- center Long-term Study to Assess the Safety and Efficacy of the Beta-3 Agonist Mirabegron (YM178) 50 mg qd and 100 mg qd in Subjects With Symptoms of Overactive Bladder

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

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

Study Design: After screening (day -21 to day -14), patients were enrolled in a 2-week, single-blind, placebo run-in period that ended at baseline (week 0). At baseline (visit 2), patients who met inclusion criteria and did not meet exclusion criteria were randomly assigned in a 1:1:1 ratio to receive mirabegron 50 mg, mirabegron 100 mg or tolterodine ER 4 mg once daily for 12 months. The randomized, double-blind, double-dummy, active-controlled treatment period consisted of visits at months 1, 3, 6, 9 and 12. Patients who completed the 12-week treatment and safety follow-up periods of studies 178-CL-046 or 178-CL-047 in any treatment group (placebo, mirabegron or tolterodine ER 4 mg) could enroll in 178-CL-049 after being off study medication for at least 30 days, as well as patients that did not participate in the 178-CL-046 or 178-CL-047 studies (naive patients) could be enrolled into this study, if they met all inclusion criteria and none of the exclusion criteria at visit 1 and visit 2.

2849 patients enrolled and 2452 patients were randomized as follows:

- Full analysis set: 2382 patients: mirabegron 50 mg: 789 patients; mirabegron 100 mg: 802 patients; tolterodine ER 4 mg 791 patients
- Full analysis set Incontinence: 1450: mirabegron 50 mg: 479 patients; mirabegron 100 mg: 483 patients; tolterodine ER 4 mg 488 patients
- Safety analysis set: 2444 patients: mirabegron 50 mg: 812 patients; mirabegron 100 mg: 820 patients; tolterodine ER 4 mg 812 patients

The inclusion/exclusion criteria were the same as the primary studies and criteria were added to accommodate precautions for the use of tolterodine. Subjects who completed Studies 178-CL-046, 178-CL-047, or who were treatment naïve were allowed to enroll.

The study had a single-blind run-in period of 2 weeks. The double-blind, active-controlled treatment period was 12 months.

The efficacy variables in this study were secondary and included:

- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of micturitions per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of incontinence episodes per 24 hours (in subjects with incontinence at baseline)
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean volume voided per micturition
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency incontinence episodes per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean number of urgency episodes (grade 3 and/or 4) per 24 hours
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in mean level of urgency
- Change from baseline to months 1, 3, 6, 9, 12 and Final Visit in the mean number of pads used per 24 hours

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

Efficacy responder analyses included:

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

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

Secondary safety variables included:

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

Statistical Methods:

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

All efficacy analyses were based on the FAS with the exception of incontinence episodes and urgency incontinence episodes, for which the FAS-I was used. For the efficacy variables derived from the micturition diary, both the actual values as well as the changes from baseline were summarized descriptively by treatment and visit (including Final Visit) using mean, SE, median, minimum, and maximum. Two models were used to analyze efficacy variables: a repeated measures model and an analysis of covariance (ANCOVA) model. Factors in the repeated measures model included previous study history, sex, geographical region, randomized treatment group, time, randomized treatment by time interaction and sex by time interaction. Co-variates in the model included baseline and baseline by time interaction. Factors in the ANCOVA model included previous study history, sex, geographical region and randomized treatment group. Baseline was the only covariate in the ANCOVA model. Both models were used to obtain adjusted mean changes from baseline along with 95% confidence intervals.

Efficacy Results: Mirabegron 50 mg and 100 mg demonstrated numeric reductions from baseline to Final Visit in mean number of micturitions per 24 hours (adjusted mean change from baseline: -1.27 and -1.41, respectively) and mean number of incontinence episodes per 24 hours in subjects with baseline incontinence (adjusted mean change from baseline: -1.01 and -1.24, respectively) as well as numeric improvements in mean volume voided per micturition (adjusted mean change from baseline: 17.5 mL and 21.5 mL, respectively). Improvements in these symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12. Both doses of mirabegron also showed numeric improvements on the additional secondary efficacy variables. Numerically similar results and a similar course of improvement over time were observed with tolterodine ER 4 mg.

Table 15: Change from Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours

	Mirabegron		Tolterodine
	50 mg (n=479)	100 mg (n=483)	SR 4 mg (n=488)
Baseline			
Mean (SE)	2.66 (0.120)	2.49 (0.113)	2.42 (0.107)
Final Visit			
Mean (SE)	1.61 (0.130)	1.26 ((0.104)	1.19 (0.094)
Change from Baseline			
Mean (SE)	-1.05 (0.102)	-1.24 (0.105)	-1.23 (0.086)

Source: Table 13, Study 178-CL-049 Report, page 96

Table 16: Change from Baseline to Final Visit in Mean Number of Micturitions Per 24 hours

	Mirabegron		Tolterodine
	50 mg (n=789)	100 mg (n=802)	SR 4 mg (n=791)
Baseline			
Mean (SE)	11.13 (0.100)	116 (0.102)	10.94 (0.093)
Final Visit			
Mean (SE)	9.85 (0.110)	9.73 ((0.113)	9.58 (0.109)
Change from Baseline			
Mean (SE)	-1.28 (0.087)	-1.43 (0.085)	-1.36 (0.087)

Source: Table 14, Study 178-CL-049 Report, page 99

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

Reviewer’s Efficacy Conclusion: In Study 049, it appears that efficacy was maintained through 12 months of mirabegron therapy.

1. ***Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:***
 - a. *total patient exposure at relevant doses that is clearly inadequate to evaluate safety*
 - b. *clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets*
 - c. *absence of a comprehensive analysis of safety data*
 - d. *absence of an analysis of data supporting the proposed dose and dose interval*

Response: No.

VII. Preliminary Safety Findings

Safety Exposure

The clinical development program consisted of studies in healthy volunteers, patients with OAB, male patients with lower urinary tract symptoms (LUTS)/BOO and patients with type 2 diabetes mellitus. A total of 29 phase 1 studies and 12 phase 2/3 studies (9 in patients with OAB, one in patients with LUTS/BOO and 2 in patients with type 2 diabetes mellitus) have been conducted globally in Europe, the United States, Canada, Japan, Australia/New Zealand and South Africa. There were a total of 8752 patients in phase 2/3 studies and 1800 healthy volunteers in phase 1 studies, of which 7325 received mirabegron. The immediate release (IR) formulation was used for the earlier phase 1 and proof of concept (POC) studies conducted in the clinical development program; all subsequent studies used the oral controlled absorption system (OCAS) formulation.

Table 17: Summary of Mirabegron Exposure: Global Phase 2/3 Population

Characteristic n(%) of Patients		Continuous Exposure of Total Mirabegron (n=5863)
Duration of Exposure (days)	≥7	5800
	≥14	5740
	≥28	5625
	≥56	5296
	≥84	4191
	≥182	1572
	≥274	1482
	≥365	622
Duration Category (days)	1-6	53
	7-13	60
	14-27	115
	28-55	329
	56-83	1105

	84-181	2619
	182-273	90
	274-364	860
	≥365	622
Duration (days)	Mean(SD)	152.0 (125.78)
	Median	85.0
	Min, Max	1, 396
Patient –years of exposure	Total	2439.44

Source: Table 10, Integrated Summary of Safety, Page 61

3.2 Patient Demographics

In the Global Phase 2/3 Population, 4399/5863 (75.0%) mirabegron patients were female. Overall, 4387/5858 (74.9%) patients were White, 1259/5858 (21.5%) were Asian, 179/5858 (3.1%) were Black or African American and 33/5858 (0.6%) were ‘Other’ ; 2655/2783 (95.4%) were not Hispanic or Latino. The percentage of Asian patients varied widely among dosage groups, ranging from 0% to 28.5% among mirabegron treatment groups, 28.3% for placebo and 39.9% for tolterodine.

The median age was 60.0 years of age; 2095/5863 (35.7%) patients were ≥ 65 years of age and 574/5863 (9.8%) patients were ≥ 75 years of age. The mean height was 164.4 cm, the mean weight was 74.78 kg and the mean body mass index (BMI) was 27.5 kg/m². The largest proportion of patients were in the < 25 kg/m² BMI group (2231/5862 [38.1%]) and were from Europe (2831/5863 [48.3%]).

Within the European/North American (EU/NA) 12 week Phase 3 Population, across all treatment groups, 3313/4611 (71.9%) were female patients. Overall, 4310/4611 (93.5%) patients were White, which is higher than that of the Global OAB 12-week Phase 2/3 Population (5220/7508 [69.5%]). Overall, 223/4611 (4.8%) patients were Black or African American, 49/4611 (1.1%) were Asian and 29/4611(0.6%) were “Other”; 2484/2633 (94.3%) of patients were not Hispanic or Latino. The median age was 61.0 years of age; 1744/4611 (37.8%) patients were ≥ 65 years of age and 499/4611 (10.8%) patients were ≥ 75 years of age. The mean height was 166.4 cm, the mean weight was 80.33 kg and the mean BMI was 29.0 kg/m². The largest proportion of patients were in the 25 to < 30 kg/m² BMI group (1715/4608 [37.2%]) and were from Europe (2565/4611 [55.6%]); all tolterodine patients (495/495 [100%]) were from Europe.

In the EU/NA Long-term Controlled Population (Study 049), the demographic and baseline characteristics (recorded at baseline for Study 178-CL-049) were consistent across treatment groups. Overall, 1810/2444 (74.1%) patients were female, 2332/2444 (95.4%) patients were White and 2367/2442 (96.9%) patients were non-Hispanic and non-Latino. The median age was 61.0 years of age. Overall, 908/2444 (37.2%) patients were ≥ 65 years of age and 239/2444 (9.8%) patients were ≥ 75 years of age. The mean height was 166.3 cm, the mean weight was 79.59 kg and the mean BMI across all treatment groups was 28.8 kg/m². The largest proportion of patients were in the 25 to < 30 kg/m² BMI group (941/2439 [38.6%]) and were from Eastern Europe (788/2444 [32.2%]).

Intrinsic and extrinsic factors were comparable across all treatment groups in the Global

OAB 12-week Phase 2/3 Population (consisting of 6 trials: Phase 3 Studies 046, 047 and 074 plus the Phase 2B multinational Studies 044, and the Japanese Phase 2 and Phase 3 Studies 044 and 048, respectively) for the 25, 50, and 100 dose groups of mirabegron.

Reviewer's Comment: The Phase 3 study population was similar to those of other approved OAB products and consisted primarily of older, White women.

3.3 Dose Rationale

The doses for Studies 178-CL-046 and 178-CL-047 were selected on the basis of the results of Study 178-CL-044 which was a phase 2b dose-ranging study in patients with OAB. In Study 178-CL-044, statistically significant and clinically relevant improvements were noted in the primary efficacy variable and most secondary efficacy variables at mirabegron doses of 50 mg to 200 mg per day compared to placebo. In Study 178-CL-044 conducted in Japan, statistically significant effects for the 25 mg dose group in the primary outcome (reduction of urinary frequency) as well as the majority of efficacy endpoints including incontinence, volume voided and urgency incontinence were demonstrated. The Sponsor was of the opinion that the findings for the 50 mg and 100 mg doses were more promising than those seen for the 25 mg dose. Therefore, they pursued doses of 50 mg and 100 mg in the Phase 3 Studies 046 and 047. However, for Study 074, at the Division's request, the Sponsor agreed to study the dose of 25 mg. The Division stated that the emerging safety profile for mirabegron appeared to show a dose-dependent pulse rate increase, with the lowest increase in the 25 mg dose group. Therefore, in study 178-CL-074, mirabegron 25 and 50 mg doses were utilized. The tolterodine ER 4 mg dose is the recommended dose in the product label.

Reviewer's comment: The dose selection is based on sound evidence from Phase 1 studies and also Phase 2 efficacy and safety studies.

3.4 Specific Populations & Pharmacokinetics

The effect of age, sex, genotype, CYP2D6, renal and hepatic impairment on the pharmacokinetics of mirabegron was studied in several single and multiple dose studies as shown below:

Age: 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) in Phase 1 studies. Similar results were obtained for the elderly population aged 65 years and above. However, population PK analysis of phase 2 and 3 data appears to indicate that age modestly affects 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 not necessary, in the Sponsor's opinion.

Sex: Mirabegron C_{max} and AUC_{tau} were approximately 40% to 50% higher, respectively, in females compared with males. The magnitude of the sex differences is attenuated with correction for body weight. 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, by Sponsor, to a higher absolute bioavailability of mirabegron in females compared to males. No dose adjustment based on sex is recommended by Sponsor; the Sponsor states that the efficacy and safety of mirabegron at the proposed therapeutic dose have been demonstrated in both males and females with OAB.

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

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 and 3 data confirmed that body weight affected mirabegron exposure. Relative to a subject with a body weight of 70 kg, AUC_{τ} was about 53% higher in a subject with a body weight of 30 kg and approximately 17% lower in a subject 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). The Sponsor concludes given documented safety of mirabegron at a 100 mg dose (twice the proposed therapeutic dose), the effect of body weight on plasma exposure is considered not clinically significant. Dose adjustment based on body weight is not necessary in the Sponsor's opinion.

Pediatric: No pediatric study has been conducted with mirabegron in the submitted development program.

Genetic Polymorphism: Genetic polymorphism for the CYP2D6 isozyme has no clinically relevant impact on mirabegron exposure. Following a single 160 mg dose of mirabegron administered as the IR formulation, mean C_{\max} and AUC_{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC_{τ} was 8% and 12% higher, respectively, in CYP2D6 poor metabolizers compared to extensive metabolizers, and mean C_{\max} values were similar between the two phenotypes. In a pooled analysis across Phase 1 studies, there was considerable overlap in exposure between the different predicted phenotypes and subjects who were poor metabolizers of CYP2D6 demonstrated AUC values in the range of those observed in extensive metabolizers. The Sponsor observes that the absence of substantial differences in exposure between poor and extensive metabolizers of CYP2D6 is consistent with the multiple elimination pathways for mirabegron.

Renal Impairment: Volunteers with renal impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and weight. Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m² as estimated using the Modification of Diet in Renal Disease [MDRD] 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 m²), 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 m²), mean C_{\max} and AUC_{inf} values were 92% and 118% higher, respectively. Although these increases in mirabegron C_{\max} and AUC_{inf} are less than achieved with doubling of the dose, the Sponsor recommends a reduction of the dose to 25 mg once daily in patients with severe renal impairment. No adjustment of the dose is being recommended in patients with mild to moderate renal impairment. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR < 15 mL/min/1.73 m², or creatinine clearance (CLcr) <15

mL/min, or patients requiring hemodialysis) and, therefore, is not recommended for use in this patient population in the Sponsor's opinion.

Hepatic Impairment: Volunteers with hepatic impairment were compared pharmacokinetically to healthy control volunteers who were matched for sex, age and body mass index (BMI). 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. Although the increase in mirabegron AUC_{inf} is less than achieved with doubling of the dose, the Sponsor recommends a reduction of the dose to 25 mg once daily in patients with moderate hepatic impairment. No adjustment of the dose is required in patients with mild hepatic impairment. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, the Sponsor is not recommended mirabegron for use in this patient population.

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. As mirabegron administration in the phase 2b and 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. Patients with OAB are considered otherwise healthy (unless age-related and other disease conditions are prevalent), and therefore a significant difference in PK characteristics of mirabegron between patients and healthy volunteers is not expected.

The effects of Extrinsic factors are discussed below:

Food: The effect of food or co-administered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of co-administered drugs were studied in several single and multiple dose studies. Co-administration of a 50 mg tablet 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 and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose according to the Sponsor. These findings are discussed extensively in a Research Report: Mirabegron and Food Effect in this NDA submission.

Effect of Co-administered Drugs: Mirabegron is cleared by multiple mechanisms (metabolism, renal and possibly biliary excretion) and drug-metabolizing enzymes, with no single predominating clearance pathway]. Therefore, co-administered drugs were expected to have a low propensity to affect the pharmacokinetics of mirabegron. These expectations have been confirmed in the DDI studies by Sponsor's interpretation.

3.5 Safety Results

Integrated Safety

This section summarizes the safety experience of the 3 pivotal studies and the long term safety study. This discussion will include adverse events of interest and the submitted “White Papers” dealing with special safety topics.

The EU/NA OAB 12-week Phase 3 Population studies included 4611 patients (2736 mirabegron, 1380 placebo and 495 tolterodine patients) who took at least one dose of double-blind study medication. In the EU/NA OAB 12-week Phase 3 Population, disposition and reasons for discontinuation of study drug were similar for all treatment groups. A total of 2429/2736 (88.8%) mirabegron, 1205/1380 (87.3%) placebo and 445/495 (89.9%) tolterodine patients completed the double-blind treatment period, while 307/2736 (11.2%) mirabegron, 175/1380 (12.7%) placebo and 50/495 (10.1%) tolterodine patients discontinued study drug. The most common primary reasons for discontinuation of study drug were AE (mirabegron: 106/2736 [3.9%]; placebo: 45/1380 [3.3%]; tolterodine: 24/495 [4.8%]) and withdrawal of consent (mirabegron: 93/2736 [3.4%]; placebo: 59/1380 [4.3%]; tolterodine: 9/495 [1.8%]).

Table 18: Listing of Deaths in Phase 3, 12 Week Population and 52 week Safety Study.

Study, Patient Number, Gender, Age, Drug Dose	MedDRA (v(12.1) Preferred Term	Onset/Day of Last Dose Mirabegron	Day of Death
Mirabegron			
178-CL-047, U000016176141 Female 66 Mirabegron 100 mg	Bladder Cancer, Colon Cancer metastatic	38/49	99
178-CL-049, 1530-6120 Female 64 Mirabegron 50 mg	Pneumonia, Acute Respiratory Failure, Multi- Organ Failure, Renal Vein Thrombosis, Staphylococcal Sepsis	107/85	108
178-CL-049, 3034-2380, female, 72, Mirabegron 50 mg	Cardiac Failure	190/190	190
178-CL-049, 3063-3438, female, 27, Mirabegron 50 mg	Completed Suicide	359/267	359
Placebo			
178-CL-046, U00015976697, female, 76	Cardiac Arrest	142/86	142
Tolterodine ER 4 mg			
178-CL-046, 3105-1598, Male, 74	Ruptured Cerebral Aneurysm	68/70	70
178-CL-049, 1836-6486, Female, 57, (12 weeks mirabegron 50 mg, 178- CL-047)	Coronary Artery Disease	208/208	208
178-CL-049, 2190-6983, Male, 68	Cerebrovascular	62/62	72

(12 weeks mirabegron 100 mg, 178-CL-047)	Accident		
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Source: Table 38, ISS, page 123

Reviewer's Comment: On preliminary review, the cases of colon cancer and suicide can not be attributed to mirabegron. The remaining two mirabegron deaths (cardiac failure, multi-system organ failure with sepsis) will be examined in greater detail as the review proceeds. Two of the deaths in the tolterodine arm had previously been on mirabegron; however, it would be difficult to attribute those events to mirabegron.

In ISS Table 39, page 127, it is notable that the mortality incidence by patient groups is lower for mirabegron than for placebo and tolterodine.

In the Global OAB 12-week Phase 2/3 Population, one or more SAE was reported for 77/4414 (1.7%) mirabegron, 38/2142 (1.8%) placebo and 16/958 (1.7%) tolterodine patients, with no apparent mirabegron dose response (see table below). The most common SAE in the total mirabegron group were atrial fibrillation (mirabegron: 5/4414 [0.1%]; placebo: 1/2142 [$< 0.1\%$]; tolterodine: 0/958), chest pain (mirabegron: 4/4414 [0.1%]; placebo: 2/2142 [0.1%]; tolterodine: 0/958) and pneumonia (mirabegron: 4/4414 [0.1%]; placebo: 1/2142 [$< 0.1\%$]; tolterodine: 0/958).

Table 19: Serious Treatment Emergent Events in Safety Analysis Set (MedDRA v12.1): Selected Preferred Terms Where Incidence Exceeds Placebo by Dose: Phase 3 EU/NA Study Population.

System Organ Class Preferred Term n (%)	Placebo N=1380	Mirabegron				Tolterodine ER 4 mg N=495
		25 mg N=432	50 mg N=1375	100 mg N=929	Total N=2736	
Overall	29(2.1)	7(1.6%)	29(2.1)	26(2.8%)	62(2.3%)	11(2.2)
Blood and Lymphatic System	0	0	0	1 (0.1)	1 (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
Supraventricular Tachycardia	0	0	0	1 (0.1)	1 (0.1)	0
Eye Disorders	0	0	1 (0.1)	0	1 (0.1)	0
Retinitis	0	0	1 (0.1)	0	1 (0.1)	0
Gastrointestinal Disorders	3 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	4 (0.1)	0
General Disorders and Administration 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
Non-cardiac Chest Pain	0	1 (0.2)	0	0	1 (<0.1)	0
Infections and Infestations	4 (0.3%)	2 (0.5)	7 (0.5%)	3 (0.3%)	12 (0.4%)	1 (0.2%)
Appendicitis	0	0	0	1 (0.1)	1 (<0.1)	0
Bronchitis	0	0	1 (0.1)	0	1 (<0.1)	0
Clostridial Infection	0	0	1 (0.1)	0	1 (<0.1)	0
Diverticulitis	0	1 (0.2)	0	0	1 (<0.1)	0

Erysipelas	0	0	0	1 (0.1)	1 (<0.1)	1 (0.2)
Gastroenteritis	0	0	1 (0.1)	0	1 (<0.1)	0
Hepatitis A	0	0	1 (0.1)	0	1 (<0.1)	0
Post Procedural Infection	0	0	1 (0.1)	0	1 (<0.1)	0
Pyelonephritis Acute	0	1 (0.2)	0	0	1 (<0.1)	0
Sepsis	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	0
Urinary Tract Infection	0	0	0	1 (0.1)	1 (<0.1)	0
Injury, Poisoning and Procedural Complications	3 (0.2%)	0	3(0.2)	4 (0.4)	7 (0.3)	1 (0.2)
Cerebral Hemorrhage Traumatic	0	0	0	1 (0.1)	1(<0.1)	0
Fall	0	0	0	1 (0.1)	1(<0.1)	1(0.2)
Humerus Fracture	0	0	1 (0.1)	0	1(<0.1)	0
Limb Injury	0	0	1 (0.1)	0	1(<0.1)	0
Open Wound	0	0	1 (0.1)	0	1(<0.1)	0
Post Procedural Hematoma	0	0	0	1 (0.1)	1(<0.1)	0
Radius Fracture	0	0	1 (0.1)	0	1(<0.1)	0
Investigations	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Cardiovascular Evaluation	0	0	0	1 (0.1)	1(<0.1)	0
Hepatic Enzyme Increased	0	0	1 (0.1)	0	1(<0.1)	0
	0	1 (0.2)	0	0	1(<0.1)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1)	0	4 (0.3)	1 (0.1)	5 (0.2)	1 (0.2)
Cervical Spinal Stenosis	0	0	1 (0.1)	0	1(<0.1)	0
Lumbar Spinal Stenosis	0	0	0	1 (0.1)	1(<0.1)	0
Osteoarthritis	0	0	1 (0.1)	0	1(<0.1)	0
Rotator Cuff Syndrome	0	0	1 (0.1)	0	1(<0.1)	0
Spinal Column Stenosis	0	0	1 (0.1)	0	1(<0.1)	0
Neoplasms Benign, Malignant	1 (0.1)	1 (0.1)	3 (0.2)	3 (0.3)	7 (0.3)	1 (0.2)
Bladder Cancer	0	0	0	1 (0.1)	1(<0.1)	0
Bowen's Disease	0	0	0	1 (0.1)	1(<0.1)	0
Breast Cancer	0	1 (0.2)	0	0	1(<0.1)	0
Colon Cancer Metastatic	0	0	0	1 (0.1)	1(<0.1)	0
Recurrent Lung Carcinoma	0	0	0	1 (0.1)	1(<0.1)	0
Malignant Melanoma	0	0	1 (0.1)	0	1(<0.1)	0

Lymph Node Metastases	0	0	1 (0.1)	0	1(<0.1)	0
Prostate Cancer	0	0	2 (0.1)	2 (0.1)		0
Nervous System Disorders	7 (0.5)	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.4)
Pregnancy, Puerperium, Perinatal	0	0	1 (0.1)	0	1 (<0.1)	0
Pregnancy	0	0	1(0.1)	0	1(<0.1)	0
Psychiatric Disorders	2 (0.1)	0	1 (0.1)	0	1 (<0.1)	0
Bipolar Disorder	0	0	1 (0.1)	0	1 (<0.1)	0
Renal and Urinary Disorders	1 (0.1)	0	3 (0.2)	3 (0.3)	6 (0.2)	0
Calculus Ureteric	0	0	0	1 (0.1)	1 (<0.1)	0
Calculus Urinary	0	0	0	1 (0.1)	1 (<0.1)	0
Hematuria	0	0	0	1 (0.1)	1 (<0.1)	0
Nephrolithiasis	0	0	1(0.1)	0	1 (<0.1)	0
Renal Failure Acute	0	0	1(0.1)	0	1 (<0.1)	0
Reproductive System and Breast Disorders	0	0	0	1 (0.1)	1 (<0.1)	0
Rectocele	0	0	0	1 (0.1)	1 (<0.1)	0
Vaginal Erosion	0	0	0	1 (0.1)	1 (<0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0	0	0	0	1 (0.2)
Surgical and Medical Procedures	3 (0.2)	0	2 (0.1)	2 (0.2)	4 (0.1)	1 (0.2)
Angioplasty	0	0	1 (0.1)	0	1 (<0.1)	0
Bunion Operation	0	0	0	2 (0.2)	1 (0.1)	0
Gastric Banding		0	1 (0.1)	0	1 (<0.1)	0
Vascular Disorders	1 (0.1)	1 (0.2)	1 (0.1)	0	2 (0.1)	1 (0.2)
Hypertensive Crisis	0	0	1 (0.1)	0	1 (<0.1)	0
Orthostatic Hypotension	0	1 (0.2)	0	0	1 (<0.1)	0

Source: Table 5.6.3.1, ISS, page 6950

Reviewer's Comments:

In the Phase 3 EU/NA Study Population, there are several review issues based on the preceding table of SAEs:

- 1. There is a small difference in incidence of atrial fibrillation as an SAE in the mirabegron group over the placebo group. This will be a review issue.*

2. *There are a total of three reports of urolithiasis as an SAE in the mirabegron group versus none in the placebo group. This will be a review issue.*
3. *There may be a difference between mirabegron and placebo in total number of infections reported as an SAE when a variety of differing infections, each reported by 1 patient, are added together. This will be a review issue.*
4. *There may be a difference between mirabegron and placebo in total number of neoplasms reported as an SAE when a variety of differing tumors, each reported by 1 patient, are added together. While not likely to represent a true treatment effect after just 3 months of treatment, this nonetheless will be a review issue.*
5. *The report of “hypertensive crisis” was evaluated and thus far, does not appear to meet criteria for “hypertensive crisis” and instead should be classified as hypertension.*
6. *There are several isolated reports of SAE injuries in mirabegron treated patients versus none with placebo. Additional information will be sought regarding each case. Factors that may have been associated with these injuries (e.g. fatigue) will be considered during the case-by-case review.*

Within Study 178-CL-049, the 52-week long-term safety study, there was not an increased incidence of atrial fibrillation in the mirabegron group compared to the tolterodine group (0.1% versus 0.4% respectively). There were four reports of liver function abnormalities (0.1 %) versus none for tolterodine. Within the SOC of Musculoskeletal and Connective Tissue Disorders 8 (0.5%) of mirabegron patients versus 2 (0.2%) of tolterodine patients reported SAEs. Within the Neoplasms, Benign and Malignant (including cysts and polyps) SOC, in the mirabegron 50 mg dose group, 1 (0.1%) reported a neoplasm SAE, and 11 (1.3%) reported a neoplasm SAE in the mirabegron 100 mg arm. In the tolterodine comparator group, 4 (0.5%) reported a neoplasm SAE. There was one report of hypertension in each of the mirabegron treatment groups (0.1%) versus none in the tolterodine group.

Reviewer’s Comments:

In Study 178-CL-049, several review issues arise from the reported SAEs:

1. *An increased incidence of atrial fibrillation SAEs in the mirabegron group compared to the tolterodine group was observed. This will be a review issue.*
2. *An increased incidence of SAEs reported as “liver function abnormalities” in the mirabegron group (n=3) compared to the tolterodine group (n=1) was observed in Study 049. This will be a review issue.*
3. *An increased incidence of SAEs reported as “neoplasms” in the mirabegron group (11 [1.3%]) compared to the tolterodine group (4 [0.5%]) was observed in Study 049. This will be a review issue.*

4. *An increased incidence of SAES reported as Musculoskeletal and Connective Tissue Disorders in the mirabegron group compared to the tolterodine group was observed. This will be a review issue.*

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%]). 0.1 % of mirabegron patients discontinued secondary to atrial fibrillation or palpitations as did similar percentage in the placebo group. 4 (0.1%) mirabegron patients discontinued due to tachycardia versus none in the placebo group. Abnormal liver function tests resulted in discontinuation in 3 (0.1%) mirabegron patients versus 1 (0.1%) placebo patient. Skin rash was reported in 2 (0.1%) of mirabegron patients leading to discontinuation versus 0 for placebo. “Hypertensive crisis” was reported in 2 (0.1%) of mirabegron 50 mg subjects.

Table 20 : EU/NA 12 Week Phase 3 Study Population TEAE Leading to Discontinuation by SOC Where Mirabegron Total Group Exceeds Placebo.

System Organ Class	Placebo N=1380	Total Mirabegron N=2736	Key Driver(s) Preferred Term (n>1)
Overall n (%)	46 (3.3)	104 (3.8)	
Cardiac Disorders	3 (0.2)	13 (0.5)	Atrial fib (3vs1) Palpitations(3vs1) Tachycardia(4vs0)
General Disorders & Administrative Site Conditions	6 (0.4)	15 (0.5)	Edema Peripheral(3vs1) Pyrexia(2vs0)
Injury, Poisoning, Procedural Complications	0	2(0.1)	
Investigations	2 (0.1)	11 (0.4)	ALT incr. (3vs1) AST incr. (3vs1) BP incr. (2vs1) Liver Test Abnormal (2vs0)
Musculoskeletal and Connective Tissue Disorders	4 (0.3)	4 (0.4)	
Pregnancy, Puerperium and Perinatal Conditions	0	1 (<0.1)	
Renal and Urinary Disorders	2 (0.1)	5 (0.2)	
Skin and Subcutaneous Disorders	2 (0.1)	12 (0.4)	
Vascular Disorders	2 (0.1)	8 (0.3)	Hypertension(6vs2) Hypertensive Crisis (2vs0)

Source: Table 5.8.3.1 ISS

Reviewer’s Comments:

In the Phase 3 EU/NA Study Population, several review issues arise from the preceding table of discontinuations due to SAEs:

- 1. The proportion of discontinuations due to liver function abnormalities and discontinuations due to “hypertension” are greater in the mirabegron group compared to the placebo group. There are also two reports of “hypertensive crisis” leading to discontinuation. These will be review issues.*
- 2. The proportion of discontinuations due to Skin and Subcutaneous adverse events is greater in the mirabegron group compared to placebo. Although no skin-related adverse event Preferred Term was reported in greater than 1 patient, there were multiple, single terms (n=5) possibly indicative of an allergic or hypersensitivity phenomenon. This will be a review issue.*
- 3. “Hypertension” was reported as an AE leading to study discontinuation in 6 mirabegron subjects versus 2 placebo subjects. This will be a review issue.*

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%]). Palpitations were noted in 2 (0.2%) of mirabegron 100 mg patients. Fatigue was a reason for discontinuation in 3 (0.4%) of mirabegron 100 mg subjects. Abnormal liver function tests were a discontinuation reason in 2 (0.2%) of mirabegron 100 mg patients and 0 mirabegron 50 mg patients. 6 (0.4%) mirabegron patients and 4 (0.5%) 50 mg patients discontinued secondary to hypertension versus 3 (0.4%) tolterodine patients. The increased incidence of neoplasms has been discussed under SAEs.

Table 21 : EU/NA Long-term Controlled Population TEAE Leading to Discontinuation by SOC Where Mirabegron Total Mirabegron Group Exceeds Tolterodine ER.4 mg.

System Organ Class	Tolterodine ER 4 mg N=812	Total Mirabegron N=1632	Key Driver(s) Preferred Term (n>1)
Overall n (%)	46(5.7)	98(6.0)	
General Disorders & Administrative Site Conditions	2 (0.2)	9 (0.6)	Fatigue (4vs1) Pain (2vs0)
Infections and Infestations	3 (0.4)	8 (0.5)	
Injury, Poisoning, Procedural Complications	1 (0.1)	5 (0.3)	
Neoplasms Benign, Malignant	1 (0.1)	7 (0.4)	Lung neoplasm malignant (2vs0) Prostate Cancer (2vs0)
Pregnancy, Puerperium and	0	1 (0.1)	

Perinatal Conditions			
Psychiatric Disorders	1 (0.1)	3 (0.2)	
Skin and Subcutaneous Disorders	1(0.1)	7(0.4)	Pruritis (2vs0) Rash (2vs1) Urticaria (2vs1)
Vascular Disorders	2 (0.1)	8 (0.3)	Hypertension(6vs2) Hypertensive Crisis (2vs0)

Source: Table 5.8.4.1 ISS

Reviewer's Comments:

In Study 178-CL-049, several review issues arise from the preceding table of adverse events leading to study discontinuation:

- 1. Fatigue was reported by 4 mirabegron subjects compared to 1 tolterodine subjects. This will be a review issue.*
- 2. Adverse events described as "liver function abnormalities", "hypertension", "neoplasms", and "Skin Disorders" have been previously identified as review issues. It appears that there are 2 reports of liver function abnormalities resulting in discontinuation in the mirabegron group. For "hypertension", 0.4% and 0.5% of subjects discontinued from the mirabegron and tolterodine groups, respectively. There appear to be 2 reports each of pruritis, rash, and urticaria in the mirabegron group.*
- 3. Palpitations and tachycardia were reported in 0.6% and 1.0 % of mirabegron patients respectively in this study. Palpitations and tachycardia will be review issues.*

In the EU/NA OAB 12-week Phase 3 Population, the most common TEAE (by PT) reported in the total mirabegron group were hypertension (mirabegron: 200/2736 [7.3%]; placebo: 105/1380 [7.6%]; tolterodine: 40/495 [8.1%]), nasopharyngitis (mirabegron: 94/2736 [3.4%]; placebo: 35/1380 [2.5%]; tolterodine: 14/495 [2.8%]) and UTI (mirabegron: 83/2736 [3.0%]; placebo: 25/1380 [1.8%]; tolterodine: 10/495 [2.0%]). In the 12-week studies, 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%]) [page 72 of Cardiovascular Research Report]. The most common TEAE in the 12-week studies 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.

Table 22: Treatment Emergent Adverse Events in 12 week Phase 3 Population (Studies 046, 047 and 074) with Incidence of 1.0% or Greater in Total Mirabegron Patients by Preferred Term, in order of frequency for the therapeutic dose of mirabegron 50 mg

Adverse Event By Preferred Term	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine ER 4 mg
	N=1380	N=432	N=1375	N=929	N=495
Overall n(%)	658 (47.7)	210 (48.6)	647 (47.1)	402 (43.3)	231 (46.7)
Hypertension	105 (7.6)	49 (11.3)	103 (7.5)	48 (5.2)	40 (8.1)
Nasopharyngitis	35 (2.5)	15 (3.5)	54 (3.9)	25 (2.7)	14 (2.8)
Headache	42 (3.0)	9 (2.1)	44 (3.2)	22 (2.4)	18 (3.6)
Urinary Tract Infection	25 (1.8)	18 (4.2)	40 (2.9)	25 (2.7)	10 (2.0)
Dry Mouth	29 (2.1)	8 (1.9)	23 (1.7)	23 (2.5)	50 (10.1)
Constipation	20 (1.4)	7 (1.6)	22 (1.6)	15 (1.6)	10 (2.0)
Diarrhea	18 (1.3)	5 (1.2)	20 (1.5)	18 (1.9)	6 (1.2)
Upper Respiratory Tract Infection	23 (1.7)	9 (2.1)	20 (1.5)	11 (1.2)	2 (0.4)
Nausea	24 (1.7)	5 (1.2)	19 (1.4)	14 (1.5)	9 (1.8)
Influenza	19 (1.4)	3 (0.7)	19 (1.4)	16 (1.7)	7 (1.4)
Bronchitis	19 (1.4)	3 (0.7)	19 (1.4)	16 (1.7)	2 (0.4)
Sinusitis	19 (1.4)	3 (0.7)	19 (1.4)	10 (1.1)	3 (0.6)
Arthralgia	15 (1.1)	7 (1.6)	18 (1.3)	6 (0.6)	2 (0.4)
Tachycardia	8 (0.6)	7 (1.6)	17 (1.2)	4 (0.4)	0
Fatigue	14 (1.0)	6 (1.4)	17 (1.2)	7 (0.8)	9 (1.8)
Back Pain	23 (1.7)	7 (1.6)	14 (1.0)	10 (1.1)	7 (1.4)
Dizziness	12 (0.9)	10 (2.3)	13 (0.9)	6 (0.6)	8 (1.6)

Source: Appendix Table 2.7.4.3.3, Summary of Clinical Safety

In the EU/NA Long-term Controlled Population (Study 049), the most common TEAE (by PT) reported in the total mirabegron group were hypertension (mirabegron 9.5%; tolterodine 9.6%), UTI (mirabegron 5.7%; tolterodine 6.4%) and nasopharyngitis (mirabegron 4.1%; tolterodine 3.1%).

Reviewer's Comment: Increased incidence of events (preferred terms) relating to altered states of consciousness, alertness or attention for mirabegron versus placebo were searched for and were not found.

Laboratory Findings:

Hematology: In the Global OAB 12-week Phase 2/3 Population, mean changes from baseline to final visit for hemoglobin and hematocrit were similar across mirabegron dose groups and similar to placebo according to the Sponsor. The mean change from baseline to final visit for platelet counts was -0.5, -5.1, -0.2, -2.7, -7.1 and -1.1 x 10⁹/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. Changes were not clinically significant in the Sponsor's opinion. The mean change from baseline to final visit for leukocyte counts decreased with increasing doses of mirabegron (-0.07, -0.07, -0.28 and -0.59 x 10⁹/L in the mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg and mirabegron 200 mg groups, respectively). The mean change from baseline to final visit for

leukocyte counts was $0.02 \times 10^9/L$ in the placebo and tolterodine groups, respectively. The Sponsor stated these changes were not clinically significant. There did not appear to be significant changes in the neutrophil, lymphocyte or eosinophil counts. The Sponsor reached similar conclusions in Study 178-CL-049 (the long term safety study).

Reviewer's Comment: There was one patient (2037-0516-mirabegron 100 mg) in Study 178-CL-049 who developed hemolytic anemia and thrombocytopenia as part of a hypersensitivity reaction at day 183. This case will be a review issue.

Chemistry: In the Global OAB 12-week Phase 2/3 Population, the mean increase from baseline to final visit for ALT was 0.3, 1.2, 0.5, 1.3, 0.8 and 0.9 U/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. The mean increase from baseline to final visit for AST was 0.3, 1.0, 0.3, 0.8, 1.1 and 0.3 U/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. The mean change from baseline to final visit in ALP (ranging from -2.1 U/L with mirabegron 200 mg to 2.9 U/L with placebo), bilirubin (ranging from -0.02 mcmmol/L with tolterodine to -0.42 mcmmol/L with mirabegron 50 mg) and GGT (-0.7 U/L with mirabegron 200 mg to 1.9 U/L with tolterodine) were generally similar across all treatment groups. The Sponsor observes that change from baseline results for hepatic chemistry parameters in the EU/NA OAB 12-week Phase 3 Population were generally consistent with those in the Global OAB 12-week Phase 2/3 Population.

In the Global OAB 12-week Phase 2/3 Population, $\leq 6.0\%$ of patients experienced any PCS (potentially clinically significant) hepatic chemistry laboratory value and the frequency was similar across treatment groups. For ALT or AST alone $\leq 1.3\%$ of mirabegron patients and 0.5% of placebo patients experienced values $> 3 \times ULN$.

Two patients, [Patient No. 178-CL-045, P00244] and [Patient No. 178-CL-049, 3353-1381], were identified as having 3-fold or more transaminase elevation combined with 2-fold or more bilirubin elevation. In one of these patients [Patient No. 178-CL-045, P00244], the criteria were met in local laboratory analysis only and the local laboratory results are not included in the database. [Patient No. 178-CL-049, 3353-1381] had ongoing viral hepatitis as an alternate etiology.

In the EU/NA Long-term Controlled Population, the mean changes from baseline to final visit for ALT, AST, ALP and total bilirubin were similar across all treatment groups. The mean change from baseline to final visit for GGT was higher in the tolterodine group compared with the mirabegron groups. The mean changes from baseline in all analytes were of small magnitude compared to the normal range of the analyte. There was a similar pattern of change over time in ALT and AST. Mean changes from baseline to final visit in ALT, AST, bilirubin, GGT and LDH were small and similar across all treatment groups, with a similar pattern of change in ALT and AST. The shifts from baseline to the highest Post-baseline ALT values represented a categorical increase for 106/678 (15.6%) mirabegron 50 mg, 92/704 (13.1%) mirabegron 100 mg and 72/700 (10.3%) tolterodine patients. Shifts from baseline to the highest post-baseline AST values represented a categorical increase for 76/744 (10.2%) mirabegron 50 mg, 61/765 (8.0%) mirabegron 100 mg and 45/755 (6.0%) tolterodine patients. In most cases, the Sponsor observes the maximum post-baseline value was ≤ 2 times the ULN. The frequency of increase from baseline to highest value for ALP, total bilirubin and GGT was generally similar across all treatment groups.

In the total mirabegron group, there were 2 patients (in the mirabegron 25 mg group) with ALT or AST > 10 x ULN. For ALT or AST, as well as for AST alone, only the placebo group had one patient with a value > 20 x ULN. Fewer than one patient per 10 patient-years of exposure had ALP > 1.5 x ULN in any treatment group; the results were the same for total bilirubin > 2 x ULN.

Reviewer's Comment: The previous data shows no specific evidence of hepatotoxicity for mirabegron. Nonetheless, the potential for hepatotoxicity (serum liver function abnormalities) was pre-defined by Sponsor as an AE of interest and will be reviewed.

With respect to BUN and creatinine in the 12 week phase 3 population the following results were noted:

Table 23: BUN and Creatinine Potentially Clinically Significant Abnormalities 12 Week Phase 3 Population.

Test	Criteria	Placebo N=1380	Mirabegron			Tolterodine ER 4 mg N=495
			25 mg N=432	50 mg N=1375	100 mg N=929	
BUN	>12.5mmol/L	12/1335 (0.9%)	3/ 418 (0.7%)	7/1328 (0.5%)	11/ 898 (1.2%)	3/ 480 (0.6%)
Creatinine	>177umol/L	0/1335	3/ 418 (0.7%)	0/1328	0/ 898	0/ 480

Source: Table 7.3.3.1, ISS/SCS, No page listed.

The Sponsor states that review of the available individual patient listings whose serum creatinine laboratory values met a PCS criterion shows that they had either abnormal values at baseline that met or were close to meeting PCS criteria and did not change substantially over the treatment course, or had an isolated PCS value at a single time point that was bracketed by normal or near baseline levels, and were not associated with any TEAE related to abnormal renal function.

Table 24: BUN and Creatinine Potentially Clinically Significant Abnormalities Long Term Controlled Population Change From Baseline

Test	Criteria	Mirabegron		Tolterodine ER 4 mg N=812
		50 mg N=812	100 mg N=820	
BUN	>12.5mmol/L	3/792 (0.4%)	7/803 (0.9%)	8/791 (1.0%)
Creatinine	>177umol/L	0/792	7/803 (0.9%)	1/791 (0.1%)

Source: Table 124, ISS, page 268.

There were no clinically significant mean changes in glucose and HbA_{1c} or blood glucose in the Phase 3 population or in the long term Controlled population.

Table 25: Glucose and HbA_{1c} 12 Week Phase 2/3 Studies Change from Baseline

Test	Criteria	Placebo n=2142	Mirabegron			Tolterodine ER 4 mg n=958
			25 mg n=811	50 mg n=2131	100 mg n=1305	
Glucose (mmol/L)	<2.5mmol/L	6/2087 (0.3%)	2/792 (0.3%)	2/2079 (0.1%)	3/1272 (0.2%)	0/939

	>11.1 mmol/L	55/2087 (2.6%)	26/792 (3.3%)	53/2079 (2.5%)	32/1272 (2.5%)	19/939 (2.0%)
HbA1c	>8%	15/1711 (0.9%)	7/418 (1.7%)	25/1704 (1.5%)	18/898 (2.0%)	10/853 (1.2%)

Source: Table 134, ISS, page 278

Table 26: Glucose and HbA1c 12 Week Long Term Controlled Population Studies Change from Baseline

Test	Criteria	Mirabegron		Tolterodine ER 4 mg N=812
		50 mg N=812	100 mg N=820	
Glucose (mmol/L)	<2.5mmol/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%)

Source: Table 135 ISS, page 278 (178-CL-049)

Hypoglycemia was infrequent occurring in 0.1% of mirabegron patients in the phase 3 population as opposed to 0.1% in the placebo population. No patient in the long term controlled study reported hypoglycemia.

Urinalysis: It is of note that in early studies, high mirabegron urinary concentrations could affect protein dipstick methodologies (Study 178-TX-049). At the proposed dose of 50 mg, mirabegron is unlikely to affect protein determinations in human urine in the Sponsor's opinion.

Across all studies in the clinical program, the Sponsor noted the absence of clinically meaningful effect of mirabegron on urinalysis parameters.

Reviewer's Comment: The potential effect of mirabegron on urine protein dipstick assessment is a review issue.

Vital Signs, Electrocardiograms and other Safety Observations:

Vital Signs:

In the EU/NA OAB 12-week Phase 3 Population, the adjusted mean change from baseline pulse rate following mirabegron at doses of 50 to 100 mg once daily was similar to or less than the adjusted mean change from baseline pulse rate following tolterodine. The adjusted mean change from baseline pulse rate in the EU/NA Long-term Controlled Population for the mirabegron 50 mg, 100 mg and tolterodine groups was 0.9, 1.6 and 1.5 bpm for AM measurements, respectively, and 0.4, 1.3 and 1.9 bpm for PM measurements, respectively. Categorical increases from baseline in pulse rate in the EU/NA OAB 12-week Phase 3 Population were noted more frequently at various cut-points with mirabegron than with placebo. Mirabegron 25 and 50 mg were comparable to tolterodine while mirabegron 100 mg demonstrated more outliers at various cut-points than tolterodine.

TEAE related to rapid pulse rate (cardiac arrhythmia, mostly tachycardia) were more frequently observed in all active treatments (2.4% to 6.6%) than placebo (1.8%) in the Global OAB 12-week

Phase 2/3 Population. The frequency of such events was comparable for all mirabegron doses of 100 mg or less (2.4% to 3.1%) and tolterodine (3.1%). In the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (3.9% and 4.1%, respectively) and was less than tolterodine (6.0%).

The overall frequency of atrial fibrillation TEAE was low (0.2%, 0.2%, 0.4%, 0.5%, 0.6% and 0.6% for placebo, mirabegron 25, 50, 100 and 200 mg, and tolterodine, respectively) and comparable for mirabegron and tolterodine in the Global OAB 12-week Phase 2/3 Population. Female patients demonstrated a generally higher increase in pulse rate compared with male patients, consistent with the approximately 40% to 50% increased exposure in female patients, although this finding was inconsistent across treatment groups and AM/PM measurements. In patients who received the proposed mirabegron therapeutic dose of 50 mg, pulse rate changes from baseline compared with placebo were approximately 1 bpm or less and pulse rate changes from baseline were similar to those in patients who received tolterodine, in both the 12-week studies and the long-term study, in both genders. Overall data suggest a greater effect of mirabegron on pulse rate in younger compared with older patients, although this finding was inconsistent.

Reviewer's Comment: The to-be-marketed dose of 50 mg appears to be associated with a pulse increase of 1 bpm upon preliminary review. The increase in pulse rate secondary to mirabegron appears to be greater in women compared to men, and in younger compared to older patients. This will be a review issue.

Blood Pressure: Mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with an approximately 1 mm Hg or less adjusted mean difference for change from baseline SBP/DBP compared with placebo. The adjusted mean difference vs placebo for change from baseline SBP in the EU/NA OAB 12-week Phase 3 Population for mirabegron 25, 50 and 100 mg and tolterodine was -0.5, 0.6, 0.4 and -0.1 mm Hg for AM measurements, respectively, and -1.0, 0.5, 0.9 and 0.0 mm Hg for PM measurements, respectively. The adjusted mean difference vs placebo for change from baseline DBP in the EU/NA OAB 12-week Phase 3 Population in mirabegron 25, 50 and 100 mg and tolterodine was -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements, respectively, and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.

In the EU/NA Long-term Controlled Population, the adjusted mean changes from baseline SBP and DBP following mirabegron 50 mg, mirabegron 100 mg and tolterodine were generally similar. The adjusted mean change from baseline for SBP in mirabegron 50 and 100 mg and tolterodine was 0.2, 0.4 and -0.5 mm Hg for AM measurements, respectively, and -0.3, 0.1 and 0.0 mm Hg for PM measurements, respectively. The adjusted mean change from baseline for DBP in mirabegron 50 and 100 mg and tolterodine was -0.3, 0.4 and 0.1 mm Hg for AM measurements, respectively, and 0.0, 0.1 and 0.6 mm Hg for PM measurements, respectively.

The Sponsor states that TEAE related to hypertension were similar for the total mirabegron (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]) groups in the EU/NA OAB 12-week Phase 3 Population. The frequency of such events was comparable for mirabegron 50 mg (120/1375 [8.7%]) or 100 mg (58/929 [6.2%]) and was highest in mirabegron 25 mg (52/432 [12.0%]). In the EU/NA Long-term Controlled Population, the occurrence of such events was comparable between mirabegron 50 and 100 mg (89/812 [11.0%]) and 83/820 [10.1%]) and tolterodine (86/812 [10.6%]).

Overall data suggested a greater effect of mirabegron on SBP/DBP in younger compared with older patients, although this finding was inconsistent. No consistent trend of SBP/DBP change was evident in patients < 65 years of age compared with patients \geq 65 years of age. In the 12-week studies, changes in adjusted mean differences vs placebo were generally similar in both age groups. In the long-term study, adjusted mean changes in AM/PM SBP were larger in patients \geq 65 years, while changes in AM/PM DBP were larger in patients < 65 years of age. This trend in the long-term study was seen in both the mirabegron and tolterodine treatment groups. In an additional analysis categorizing patients into < 45 years, \geq 45 to < 65 years and \geq 65 years of age, change from baseline and adjusted mean difference vs placebo in change from baseline SBP/DBP was generally smaller in older compared with younger patients who received mirabegron, with the greatest change generally seen in patients < 45 years of age. This trend was also seen in the adjusted mean change from baseline SBP/DBP measurements in the long-term study. Patients who received mirabegron 50 mg, the proposed therapeutic dose, had an adjusted mean difference vs placebo and an adjusted mean change from baseline SBP/DBP of approximately 1 mm Hg or less in the 12-week studies and the long-term study, respectively, comparable to tolterodine in both younger and older patients.

Reviewer's Comment: The mean increase in blood pressure of approximately 1 mm Hg over placebo observed with mirabegron will be a review issue.

ECGs: Excluding the QT interval, the Sponsor states there are generally no trends observed in the ECG intervals across treatments and subgroups in either the EU/NA OAB 12-week Phase 3 Population or the EU/NA Long-term Controlled Population. The Sponsor also states there are also no consistent trends for ECG abnormalities, except for mirabegron-related changes due to increased heart rate, and selected arrhythmia, mostly reported as sinus tachycardia.

In the Sponsor's initial QT Study (178-CL-037), post-hoc analyses showed that the original analysis did not adequately correct for mirabegron-induced increases in heart rate. When the Sponsor reanalyzed the results using multiple corrections for pulse rate, it appeared that mirabegron in females at 200 mg had a mean treatment difference of 15.05 msec when compared to placebo (upper bound of 95% CI = 18.01 msec). To resolve this issue, the Sponsor initiated a repeat TQT study (178-CL-077) with 352 subjects. In the overall population (both female and male volunteers), at the therapeutic dose of mirabegron (50 mg), the mean treatment difference was below 5 msec and the upper bound of the 1-sided 95% CI for the QTcI interval was less than 10 msec at all evaluated time points. At the suprathreshold dose of mirabegron 100 mg, the mean treatment difference was above 5 msec at 3.0 to 4.5 hour time points and upper bound of the 1-sided 95% CI for the QTcI interval was less than 10 msec at all evaluated time points. At a higher suprathreshold dose (mirabegron 200 mg) the point estimate was above 5 msec at all evaluated time points and the upper bound of the 1-sided 95% CI did not exceed 10 msec at any evaluated time points.

Therefore, in Study 077, based upon this preliminary review, mirabegron did not cause QTcI prolongation at the proposed therapeutic dose of 50 mg or the suprathreshold 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. At the 200 mg dose, which increased C_{max} and AUC by approximately 8.4- and 6.5-fold, respectively compared to the therapeutic dose, the mean increase in QTc was > 5 msec at all timepoints, but the upper bound of the 95% CI did not exceed 10 msec at any timepoint.

However, in Study 077, in a subgroup analysis by gender, mirabegron prolonged the QTc interval in female volunteers at the suprathreshold dose of 200 mg. At the 200 mg mirabegron dose, the maximum increase of QTc1 was 10.42 msec. The 90% CI (at 5 hours) was 7.40, 13.44 msec. In this study, in male volunteers, mirabegron 50 mg, 100 mg and 200 mg did not produce QTc interval prolongation. At mirabegron doses of 50 mg and 100 mg, at no timepoint did the 90% CI go above 10 msec in female subjects. Of note, female volunteers had approximately 30% to 60% higher mean Cmax and 40% to 50% higher mean AUCtau of mirabegron than male volunteers.

Reviewer's Comment: The increase in QTc in females dosed with 200 mg mirabegron is a review issue. The Interdisciplinary Review Team- QT (IRT/QT) has been asked to review these results.

The Sponsor's summary of ECG data includes:

- All mirabegron treatment groups had a decrease in mean QTcF from baseline to 12 weeks of approximately 2 msec; the decrease observed for mirabegron 200 mg was slightly larger at 4.4 msec.
- There was a higher occurrence of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo. QTc measurements exceeding these thresholds occurred with similar frequency in patients receiving mirabegron 25, 50 and 100 mg and placebo.
- Maximum QTcF values > 450 msec occurred more often in female than male patients with a comparable frequency in all treatment groups except for mirabegron 200 mg. No differences were observed between male and female patients in the frequency of maximum change from baseline in QTcF of ≥ 30 msec.
- Elderly OAB patients (≥ 65 years of age) had a higher frequency of maximum QTcF values > 450 msec; the frequency of maximum changes from baseline > 30 msec were similar for patients < 65 years and ≥ 65 years of age.
- There were few SAE, TEAE and CV adjudicated events that involved QT prolongation or ventricular arrhythmias and there was no difference between the frequency of these events in the mirabegron, placebo, and tolterodine groups. No events of torsades de pointes were reported in any patient in the mirabegron clinical program.

Reviewer's Comment: The increased incidences of QTcF > 450 msec in patients receiving mirabegron compared to placebo will be a review issue. The increased incidences of QTcF in females compared to males and in elderly (≥ 65 years) compared to non-elderly (< 65 years) will also be review issues.

PVR Volume: In the Global OAB 12-week Phase 2/3 Population, the mean change from baseline to final visit in PVR volume was ≤ 3 mL and comparable across all treatment groups; no dose response was observed. The mean change from baseline to final visit in PVR volume and shifts from a baseline PVR volume in the EU/NA OAB 12-week Phase 3 Population were consistent with the Global OAB 12-week Phase 2/3 Population. For Global OAB 12-week Phase 2/3 Population, mean baseline PVR volume was higher for patients with a history of BPH (32.1 to 42.6 mL) compared with patients without a history of BPH (21.5 to 27.8 mL), across all treatment groups, except for mirabegron 200 mg (in which n = 4 for patients with a history of BPH and n = 8 for patients without a history of BPH). There were no notable differences between the patients with or without a history of BPH in change from baseline to final visit in PVR volume.

Urodynamics: Study 178-CL-060 was a randomized, double-blind, parallel group, placebo-controlled, multicenter study designed to assess the urodynamic safety of mirabegron 50 and 100 mg once daily for 12 weeks in male patients (≥ 45 years of age) with LUTS and BOO, a population at risk for developing urinary retention. The primary variables measured in the study were cystometric urodynamic safety variables: maximum flow rate (Qmax) and detrusor pressure at maximum flow rate (PdetQmax), both may be considered measures of urinary obstruction. Urodynamic safety results demonstrated that treatment with mirabegron 50 mg and 100 mg once daily did not result in a decrease in Qmax or an increase in PdetQmax in patients with LUTS and BOO compared with treatment with placebo. One placebo subject and one mirabegron subject experienced retention in the study.

Intrinsic Factors and Their Potential Impact on Safety:

Gender: In the Global OAB 12-week Phase 2/3 Population, although TEAE were generally reported more frequently in female patients compared with male patients across treatment groups, the difference from placebo was generally similar between genders. In the EU/NA Long-term Controlled Population (Study 049), the frequency of TEAE was similar between genders across groups. Hypertension was the most frequently reported TEAE for both genders and was reported with similar frequency in the mirabegron and tolterodine groups and was more frequent among males than females in all treatment groups.

Table 27: TEAE by Gender in the Global OAB 12 Week Phase 2/3 Population

Gender	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Tolterodine ER 4 mg
Female n	1647	610	1630	999	155	744
Male n	495	201	501	306	12	
Overall (%)	1182 (55.2)	452 (55.7)	1173 (55.0)	654 (50.1)	80 (47.9)	577 (60.2)
Female	933 (56.6)	349 (57.2)	919 (56.4)	515 (51.6)	75 (48.4)	461 (62.0)
Male	249 (50.3)	103 (51.2)	254 (50.7)	139 (45.4)	5 (41.7)	116 (54.2)

Source: Table 160, ISS, page 324.

The Sponsor reports that the frequency of SAE by gender was similar across treatment groups in both Phase 3 studies and EU/NA Long-Term Controlled Population.

In the Global OAB 12-week Phase 2/3 Population, the frequency of TEAE leading to permanent discontinuation of study drug was generally similar across treatment groups in both genders. The most common TEAE (by PT) leading to permanent discontinuation of study drug in the total mirabegron group (including doses of mirabegron from 25 mg to 200 mg) were headache (mirabegron 0.3%; placebo 0.2%; tolterodine 0.3%), constipation (mirabegron 0.2%; placebo 0.1%; tolterodine 0.1%) and hypertension (mirabegron 0.2%; placebo 0.1%; tolterodine 0.1%) for female patients, and hypertension (mirabegron 0.4%; placebo 0.2%; tolterodine 0/214) for male patients. Similar findings occurred in the long-term study population. Frequency of TEAE was generally higher in female patients compared with male patients across treatment groups, though hypertension, one of the most frequent TEAE in every population, was generally observed

more in male patients than female patients. The incidence of “hypertension” as an AE in the 12 week EU/NA Phase 3 study population for the 50 mg dose group was 6.1% (N=982) for females, 10.9% (N=393) for males versus 7.0% and 9.3% for placebo respectively.

Reviewer’s Comments:

- 1. In the Global OAB 12-Week Population, the frequency of TEAEs was generally higher in female patients compared with male patients across treatment groups. This will be a review issue.*
- 2. The incidence of hypertension in the EU/NA OAB 12 week Population was greater in males than in females in both placebo and active arms. This will be a review issue.*

Age: 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.

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 OAB 12-week Phase 3 Population and 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 12-week and long-term studies, 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.

Reviewer’s Comment: In the Global OAB 12-Week Phase 2/3 Population, the frequency of serious adverse events and discontinuations due to adverse events was generally higher in patients > 65 years of age and > 75 years of age compared to patients ≤ 65 years of age and ≤ 75 years of age, respectively. This will be a review issue.

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, conclusions regarding TEAE according to race cannot be drawn by the Sponsor.

BMI: In the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations, the overall frequency of TEAE generally increased with increasing BMI. The frequency of SAE increased as BMI increased in the EU/NA Long-term Controlled Population, but was similar in the 12-week studies; the frequency of TEAE leading to permanent discontinuation of study drug was similar across BMI categories.

BPH: 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. The frequency of UTI TEAE by history of BPH was examined. Although the rates of UTI were generally higher in male patients with BPH history compared with males without BPH, the pattern of 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 by the Sponsor’s analysis. There were no notable differences between the patients with or without a history of BPH in change from baseline to final visit in PVR volume.

Extrinsic Factors and Their Potential Impact on Safety

Geographical Region: In the Global OAB 12-week Phase 2/3 Population, the frequency of TEAE was numerically higher in Japan compared with Europe and North America across treatment groups (there were no tolterodine-treated patients in the North American population). The Japanese phase 2/3 studies had higher proportions of patients with abnormal laboratory AE, since any abnormal value representing at least a 20% worsening from baseline was required by protocol to be reported as an AE [Section 3.3.2.1]. Thus, the proportion of patients with AE in the EU/NA OAB 12-week Phase 3 Population is lower than in the Global OAB 12-week Phase 2/3 Population, since the latter population included Japanese phase 2/3 studies.

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.

In the Global OAB 12-week Phase 2/3 Population, the frequency of SAE was similar across treatment groups in Europe and North America and Japan, except that North America did not have any patients treated with tolterodine. In the EU/NA OAB 12-week Phase 3 Population and the EU/NA Long-term Controlled Population, Europe and North America had a similar frequency of SAE for all treatment groups except in the tolterodine group, which was not represented in North America.

In the 12-week studies, in the regions that had enough patients to evaluate, the frequency of permanent discontinuation of study drug was similar across regions and treatment groups. The frequency of permanent discontinuation of study drug was higher in the EU/NA Long-term Controlled Population.

Fed/Fasting (Food) Status: Sponsor concluded that mirabegron can be taken with or without food at the proposed therapeutic dose of 50 mg. They have submitted in this NDA application a research report “Mirabegron and Food Effect.” The Sponsor observes, “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. This differential drug adsorption based on meal components may largely contribute to the reduced bioavailability of mirabegron observed when administered with a low fat meal. 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; the absorption of mirabegron therefore can be dictated by how much drug arrives at various parts of the digestive tract over what time periods and in what concentrations. The available data indicate that the effect of food status (fed or fasted) is of limited clinical relevance and do not support additional instructions for dosing relative to meal intake. Mirabegron can be administered at the proposed therapeutic dose with or without food.”

Reviewer’s Comment: We await the review of these fed/fasted data by the Office of Clinical Pharmacology.

Alpha Blockers: In the EU/NA OAB 12-week Phase 3 Population; the use of alpha 1-AR antagonists at baseline was associated with a lower frequency of TEAE in the total mirabegron and placebo groups; this was also the case in the total mirabegron and tolterodine groups in the EU/NA Long-term Controlled Population (Study 049). 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 and long-term controlled studies than without baseline use. Overall, the frequency of hypertension was generally higher among users of alpha 1-AR antagonists across treatment groups compared to nonusers. The frequency of cardiac arrhythmia, UTI, urinary retention, syncope, postural hypotension and falls, was generally similar among users of alpha 1-AR antagonists and nonusers. Mean changes from baseline in PVR volume were also consistent among users and nonusers of alpha 1-AR antagonists. In the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Populations, no patients with baseline use of alpha 1-AR antagonists experienced a urolithiasis, seizure or glaucoma TEAE

Reviewer's Comment: In the EU/NA OAB 12-Week population, the frequency of SAEs and discontinuations due to AEs was generally higher in patients who were using alpha-1 AR antagonists (alpha-1 blockers) at baseline compared to those not using alpha-1 blockers at baseline. This will be a review issue.

Special Safety Topics:

This section is a preliminary analysis of Special Safety Topics/Adverse Events of Interest. Some of the information in this section is derived from Research Reports for specific safety topics of interest that were submitted by Sponsor in the NDA.

Cardiovascular Safety

As a beta-3 adrenergic agonist, mirabegron may act on the vasculature. Tachycardia has been reported as a clinical adverse event and there appears to be a modest effect on increasing both pulse and blood pressure. Therefore, Cardiovascular Safety is of interest:

This section consists of excerpts and information from the Sponsor's Research Report: "Mirabegron and Cardiovascular Safety":

Effects of mirabegron on blood pressure and pulse:

- In clinical studies, increases in pulse rate and blood pressure occurred primarily in patients and volunteers treated with a suprathreshold dose of mirabegron 200 mg, a dose associated with an approximately 8.4- and 6.5-fold increase in C_{max} and AUC_{tau} compared with the therapeutic 50 mg dose.
- In the OAB population, a mean change of approximately 1 beat per minute (bpm) for pulse rate and approximately 1 mm Hg or less for systolic/diastolic blood pressure (SBP/DBP) was observed in patients who received the therapeutic dose of mirabegron 50 mg, as assessed by measurements made by patients (using a self-measurement device) and recorded in patient diaries, as well as measurements made at clinic visits. This magnitude of change was similar for both 12-week and long-term studies, for men and women, and in the mirabegron and tolterodine treatment groups.
- In patients with OAB, categorical increases in pulse rate were noted more frequently with mirabegron and tolterodine than with placebo, with similar changes observed for mirabegron 50 mg and tolterodine.
- Categorical increases in SBP/DBP were similar in the placebo, mirabegron and tolterodine treatment groups.

- Mirabegron-related changes in pulse rate and blood pressure were more apparent in healthy volunteers than in OAB patients. The majority of OAB patients in the phase 2/3 studies were > 55 years of age, whereas the majority of healthy volunteers in the phase 1 studies were young (30 years or younger). While yet to be determined, age may play a role in the vasoactivity of mirabegron.
- Treatment emergent adverse events (TEAE) and serious adverse events (SAE) coded as “hypertension” were similar for mirabegron 50 mg, placebo, and tolterodine in the EU/NA OAB 12-week studies, and were similar for mirabegron and tolterodine in the long-term study. TEAEs coded as “hypertension” were reported by 8.4%, 8.5% and 9.7% of mirabegron (all doses combined), placebo, and tolterodine subjects, respectively. The frequency of “hypertension” reported as a TEAE was comparable for mirabegron doses of 50 mg (8.7%) or 100 mg (6.2%), and was highest in mirabegron 25 mg group (12.0%).
- In the EU/NA 12-Week OAB population, two TEAEs of “hypertension” were reported as SAEs: Patient No. 3028-2446 in Study 46 with “hypertensive crisis” on mirabegron 50 mg, and Patient No 3313-3207 with “hypertension” on tolterodine.
- In the EU/NA 12-Week OAB population, a total of 15 patients discontinued study drug due to a TEAE of “hypertension”. Overall, the frequency of “hypertension” leading to discontinuation was higher in the mirabegron group (all doses) (0.4%), compared with placebo (0.2%) and tolterodine (0.2%).
- In the EU/NA Long-term Controlled Population (Study 049), the occurrence of “hypertension” reported as a TEAE was comparable between mirabegron 50 and 100 mg (11.0% and 10.1%, respectively), and tolterodine (10.6%).
- In the EU/NA Long-term Controlled Population (Study 049), two TEAEs coded as “hypertension” were reported as an SAE: Patient No. 3019-0364 with “hypertension” in the 50 mg group, and Patient No. 1630-7319 with “hypertension” in the 100 mg group.
- In the EU/NA Long-term Controlled Population (Study 049), the frequency of TEAE of “hypertension” leading to discontinuation was similar for the total mirabegron group (0.4%) and for tolterodine (0.5%).

Reviewer’s Comments:

1. *The increase in blood pressure and pulse related to mirabegron, and its clinical significance, will be review issues.*
2. *Overall, the frequency of “hypertension” leading to discontinuation in the EU/NA 12-Week OAB Population was higher in the mirabegron (all doses) group (0.4%), compared to placebo (0.2%) and tolterodine (0.2%). This will be a review issue.*

Effects of mirabegron on QT:

- There appeared to be no clinically meaningful changes in corrected QT interval (QTc) observed at the proposed mirabegron therapeutic dose of 50 mg. At the suprathreshold dose of 200 mg, a dose which increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold relative to the therapeutic dose of 50 mg, there were increases from baseline in the mean corrected QT interval (QTcI) of > 5 msec, with the largest QTcI treatment effect

occurring at 4 to 5 hours, with a mean (upper bound of the 1-sided 95% CI) treatment difference of 8.21 (9.99) msec in all volunteers, 10.42 (13.44) msec in female volunteers and 7.33 (9.42) in male volunteers.

- In the Global OAB 12-week Phase 2.3 Population:
 - Adverse Events possibly related to QTc prolongation were reported in 4/4414 (0.1%) total mirabegron patients, 2/2142 (0.1%) placebo patients and 2/958 (0.2%) tolterodine patients. None of these led to study discontinuation.
 - No adverse events of ventricular tachycardia, ventricular fibrillation or torsades de pointes were reported in these 12-week studies. One SAE of “loss of consciousness” was reported (Patient P07504 in Study 048).
- In the EU/NA Long-term Controlled Population (Study 049):
 - Adverse events possibly related to QTc prolongation were reported in 3/812 (0.4%) mirabegron 50 mg patients, 2/820 (0.2%) mirabegron 100 mg patients and 3/812 (0.4%) tolterodine patients.
 - One SAE possibly related to QTc prolongation was reported amongst 812 (0.1%) patients in the mirabegron 50 mg group. The SAE was cardiac arrest, ventricular fibrillation and ventricular tachycardia. This event was adjudicated by the Sponsor’s Cardiovascular Adjudication Committee as a nonfatal myocardial infarction. There was also 1/812 (0.1%) patients in the tolterodine group in whom “cardiac arrest” was reported. The Sponsor’s Cardiovascular Adjudication Committee attributed this event to ventricular fibrillation.

Reviewers Comments:

1. *The degree of QT prolongation in association with mirabegron will need further review.*
2. *The single case of cardiac arrest with ventricular tachycardia and ventricular fibrillation in a mirabegron-treated patient in Study 049 will be a review issue.*

Other clinical adverse events related to the cardiovascular system (including a brief overview analysis of reported major adverse cardiovascular events [MACE], adverse events related to rapid pulse [cardiac arrhythmia, such as sinus tachycardia and atrial fibrillation], and syncope):

- The Sponsor states that the blinded, external Cardiovascular Adjudication Committee reviewed clinical adverse events in trials of mirabegron, and they found that the proportion of patients with at least one adjudicated-confirmed cardiovascular adverse event was similar across placebo, mirabegron and tolterodine treatment groups.
- The Sponsor states that small changes in vital signs, predominantly pulse rate, are not unprecedented for OAB therapies and these small changes did not result in more cardiovascular adverse events (AE) and APTC/MACE events in the mirabegron treatment groups as compared with other treatments (placebo and tolterodine).
- The Sponsor states that in the Global OAB 12-week Phase 2/3 Population, the incidence of Major Cardiovascular Adverse Events (MACE) was low and comparable between treatment groups:
 - Events adjudicated as MACE occurred in 4/2142 (0.2%) patients in the placebo group (3 as nonfatal stroke and one as cardiovascular death), 2/811 (0.2%) patients in the mirabegron 25 mg group (both as nonfatal stroke) and 1/958

- (0.1%) patient in the tolterodine group (cardiovascular death). There were no such reports in the therapeutic dose groups (mirabegron 50 mg) in the 12-Week studies 046, 047 and 074.
- Among all mirabegron patients (all doses) in the Global OAB 12-Week Phase 2/3 population, the relative risk (RR) compared with placebo for the occurrence of APTC/MACE cardiovascular events was 0.24 (95% CI: 0.02, 1.69).
 - The proportion of mirabegron-treated patients with 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 Sponsor states that in EU/NA Long-Term Controlled Population (Study 049), the incidence of MACE was also low and comparable between treatment groups::
 - Events adjudicated as MACE 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. The events in the mirabegron 50 mg patients were nonfatal stroke (3 patients), nonfatal myocardial infarction (2 patients) and cardiovascular death (one patient). In the tolterodine patients, the events were cardiovascular death (2 patients), a nonfatal myocardial infarction (one patient) and a nonfatal stroke (one patient).
 - Among all mirabegron patients, the RR compared with tolterodine for the occurrence of MACE was 0.75 (95% CI: 0.18, 3.60).
 - The proportion of mirabegron-treated patients with 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 mirabegron patients.
 - The Sponsor states that in the Global OAB 12-Week Phase 2/3 Population there was an increased incidence of adverse events related to rapid pulse due to mirabegron:
 - TEAEs related to rapid pulse rate (cardiac arrhythmia, mostly sinus tachycardia) were more frequently observed in all active treatments (mirabegron 25 mg 3.1%, mirabegron 50 mg 2.6%, mirabegron 100 mg 2.4%, and mirabegron 200 mg 6.6%) than in placebo (1.8%).
 - The proportion of patients with atrial fibrillation reported 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 permanent discontinuation of study drug.
 - The overall occurrence of tachycardia events in the EU/NA OAB 12-week Phase 3 Population, either based on TEAE or observations of pulse rate ≥ 100 bpm captured by patient diary, was 48/1380 (3.5%) placebo, 22/432 (5.1%) mirabegron 25 mg, 57/1375 (4.1%) mirabegron 50 mg, 46/929 (5.0%) mirabegron 100 mg and 16/495 (3.2%) tolterodine patients.

Reviewer's Comments:

1. *On preliminary review, it appears that mirabegron is associated with an increased risk of tachycardia as compared to placebo and tolterodine.*
 2. *TEAEs related to rapid pulse rate (cardiac arrhythmia, mostly sinus tachycardia) will be a review issue.*
 3. *The independent role of mirabegron in atrial fibrillation will be a review issue.*
- The Sponsor states that in the EU/NA Long-term Controlled Population (Study 049), the occurrence of adverse events related to rapid pulse was low and similar between treatment groups:
 - The occurrence of TEAE coded as “cardiac arrhythmia” was comparable between mirabegron 50 and 100 mg (3.9 and 4.1%, respectively) and was less than tolterodine (6.0%).
 - 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 permanent discontinuation of study drug.
 - The overall occurrence of tachycardia events either based on TEAE or observations of pulse rate ≥ 100 bpm captured by patient diary, was 28/812 (3.4%) for mirabegron 50 mg, 50/820 (6.1%) for mirabegron 100 mg and 55/812 (6.8%) for tolterodine patients.

Reviewer's Comment: The incidence of tachycardia in mirabegron 50 mg patients was less than that of tolterodine, but we do not know if subjects with tachycardia in the pivotal studies elected not to continue in the long-term study.

- There appeared to be no signal of increase in cardiac failure in either the Global OAB 12-Week Phase 2/3 Population or in the EU/NA Long-Term Controlled Population:
 - In the Global OAB 12-week Phase 2/3 Population, TEAE of CHF based on the SMQ of cardiac failure occurred in 14/2142 (0.7%), 4/811 (0.5%), 14/2131 (0.7%), 15/1305 (1.1%), and 5/958 (0.5%) patients in 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 edema not elsewhere classified (NEC) (29/33 patients in the total mirabegron group).
- In the EU/NA Long-term Controlled Population, TEAE of CHF based on the SMQ of cardiac failure occurred in 10/812 (1.2%), 6/820 (0.7%) and 9/812 (1.1%) patients for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. The majority of cardiac failure TEAE were from the HLT of edema NEC (12/16 patients in the total mirabegron group).
- As a beta-3 receptor antagonist is important to determine whether mirabegron acts on human vasculature and if so, to what degree. Therefore, in addition to assessments of blood pressure and pulse, as well as clinical cardiovascular AEs, the specific adverse event of syncope was analyzed. In addition to events coded as syncope, this analysis also captures 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).

- In the Global OAB 12-week Phase 2/3 Population, one or more syncope, postural hypotension and falls events were reported by 90/4414 (2.0%) mirabegron, 35/2142 (1.6%) placebo and 14/958 (1.5%) tolterodine patients, with no apparent mirabegron dose response. The majority of events were under the category of falls; one or more syncope or postural hypotension events was reported by ≤ 0.1% of patients for both total mirabegron and placebo; there were no events reported with tolterodine. One or more events of falls was reported by 86/4414 (1.9%) mirabegron, 32/2142 (1.5%) placebo and 14/958 (1.5%) tolterodine patients, with no apparent mirabegron dose response. The most common TEAE (by PT) in the total mirabegron group under the category of falls was contusion (mirabegron: 13/4414 [0.3%]); placebo: 8/2142 [0.4%]; tolterodine: 4/958 [0.4%]). One or more SAE of syncope, postural hypotension and falls were reported by 9/4414 (0.2%) mirabegron, 4/2142 (0.2%) placebo and 2/958 (0.2%) tolterodine patients, with no apparent mirabegron dose response. One placebo patient reported an SAE of syncope and one mirabegron patient reported an SAE of postural hypotension; the remaining SAE consisted of “Falls.” One or more SAE under the category of falls was reported by 8/4414 (0.2%) mirabegron, 3/2142 (0.1%) placebo and 2/958 (0.2%) tolterodine patients, with no apparent mirabegron dose response.

- One or more SAE of syncope, postural hypotension and falls were reported by 9/4414 (0.2%) mirabegron, 4/2142 (0.2%) placebo and 2/958 (0.2%) tolterodine patients, with no apparent mirabegron dose response. One placebo patient reported an SAE of syncope and one mirabegron patient reported an SAE of postural hypotension; the remaining SAE consisted of “Falls.” One or more SAE under the category of falls was reported by 8/4414 (0.2%) mirabegron, 3/2142 (0.1%) placebo and 2/958 (0.2%) tolterodine patients, with no apparent mirabegron dose response. One or more TEAE under the category of falls was reported in 68/1632 (4.2%) mirabegron patients (mirabegron 50 mg: 38/812 [4.7%]; mirabegron 100 mg: 30/820 [3.7%]) and 40/812 (4.9%) tolterodine patients. The most common TEAE (by PT) in the total mirabegron group was fall (mirabegron: 8/1632 [0.5%]; tolterodine: 5/812 [0.6%]). One or more syncope, postural hypotension and falls SAE was reported in 8/1632 [0.5%] mirabegron patients (mirabegron 50 mg: 4/812 [0.5%]; mirabegron 100 mg: 4/820 [0.5%]) and 2/812 (0.2%) tolterodine patients. All of these SAE were under the category of falls; there was no SAE of syncope or postural hypotension [ISS Table 6.6.2.3]. None of the SAE led to permanent discontinuation of study drug and none of the SAE in the mirabegron-treated patients were assessed as related to the study drug. One or more syncope, postural hypotension and falls TEAE leading to permanent discontinuation of study drug was reported in 4/1632 [0.2%] mirabegron patients (mirabegron 50 mg: 3/812 [0.4%]; mirabegron 100 mg: 1/820 [0.1%]) and 1/812 (0.1%) tolterodine patients. All of these events were under the category of falls; there were no patients who reported a syncope or postural hypotension TEAE leading to permanent discontinuation of study drug.

Reviewers Comment: No real association between falls, trauma, syncope or postural hypotension and mirabegron use is discerned in this preliminary review.

Seizure-Type Events

Seizures were specifically analyzed as adverse events of interest as an imbalance in frequency of seizures between treatment groups could be a sequelae of a potential proarrhythmic effect of an investigational drug.

In the entire phase 2/3 program, 3 patients reported a TEAE (all considered by the investigator as serious) in the Convulsions SMQ (used to identify seizure as an AE of interest): 2 patients treated with placebo and one patient treated with tolterodine. No mirabegron patient in phase 2/3 studies reported a TEAE in the Convulsions SMQ. There was one mirabegron volunteer [Volunteer No. 178-CL-072, S1019] in the Global Phase 1 Population who reportedly experienced a seizure.

Urinary Tract Events (UTI, Urinary Retention, Urolithiasis)

The Sponsor has identified the following potential risks of treatment in patients with OAB, specifically: 1) UTIs are frequent comorbid conditions in patients with OAB; 2) Patients with OAB and co-morbid urological conditions that potentially limit bladder outflow may be at risk for urinary retention, and 3) 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.

- **UTI**

In the Global OAB 12-week Phase 2/3 Population:

One or more UTI TEAEs was reported in 191/4414 (4.3%) mirabegron, 65/2142 (3.0%) placebo and 42/958 (4.4%) tolterodine patients, with no apparent mirabegron dose response. The most common UTI TEAE (by PT) in the total mirabegron group was UTI (mirabegron: 103/4414 [2.3%]; placebo: 30/2142 [1.4%]; tolterodine: 13/958 [1.4%]), cystitis (mirabegron: 55/4414 [1.2%]; placebo: 21/2142 [1.0%]; tolterodine: 21/958 [2.2%]) and dysuria (mirabegron: 17/4414 [0.4%]; placebo: 5/2142 [0.2%]; tolterodine: 6/958 [0.6%]). One or more UTI SAE was reported in 2/4414 (< 0.1%) mirabegron patients (one patient with pyelonephritis acute for mirabegron 25 mg, one patient with UTI for mirabegron 50 mg) and 1/958 (0.1%) tolterodine patients (pyelonephritis acute); no events were reported for placebo. One or more UTI TEAE leading to permanent discontinuation of study drug was reported by 1/4414 (< 0.1%) mirabegron patient (one patient with both bladder pain and urethral pain for mirabegron 25 mg), 1/2142 (< 0.1%) placebo patient (one patient with UTI) and 2/958 (0.2%) tolterodine patients (one patient with cystitis and one patient with pyelonephritis acute).

In the EU/NA Long-term Controlled Population:

One or more UTI TEAE was reported in 143/1632 (8.8%) mirabegron patients (mirabegron 50 mg: 74/812 [9.1%]; mirabegron 100 mg: 69/820 [8.4%]) and 81/812 (10.0%) tolterodine patients. The most common UTI TEAE (by PT) in the total mirabegron group were UTI (mirabegron: 93/1632 [5.7%]; tolterodine: 52/812 [6.4%]), cystitis (mirabegron: 28/1632 [1.7%]; tolterodine: 19/812 [2.3%]) and dysuria (mirabegron: 13/1632 [0.8%]; tolterodine: 4/812 [0.5%]). There were no reports of UTI SAE for patients who received mirabegron. There was 1/812 (0.1%) tolterodine patient who reported a UTI SAE. One or more UTI TEAE leading to permanent discontinuation of study drug was reported by 5/1632 (0.3%) mirabegron patients (3 patients with UTI for mirabegron 50 mg and 2 patients with dysuria for mirabegron 100 mg) and 2/812

(0.2%) tolterodine patients (one patient with pyelonephritis and the patient with UTI discussed above).

The Sponsor states that patients with BPH are not at increased risk for UTI with mirabegron. UTI was more common in women, the elderly and patients with diabetes.

Reviewer's Comment: There appears to be an association of UTI with mirabegron use in OAB patient as compared to placebo subjects. This will be a review issue.

- Urinary Retention

In the Global OAB 12-week Phase 2/3 Population:

One or more urinary retention TEAEs was reported by 2/4414 (< 0.1%) mirabegron, 7/2142 (0.3%) placebo and 3/958 (0.3%) tolterodine patients, with no apparent mirabegron dose response. Within the three pivotal studies, overall, few TEAE of acute retention of urine were reported across treatment groups and the frequency was lower in the mirabegron group than in the placebo or tolterodine treatment groups. One patient reported a TEAE (by lower level term [LLT]) of acute retention of urine in the mirabegron 50 mg group; 3 patients each in the placebo and tolterodine groups also reported this event. No AE of acute retention of urine were observed in mirabegron-treated patients in Studies 178-CL-047 and 178-CL-074, where patients at risk for acute retention of urine were not specifically excluded. One patient treated with placebo [Patient No. 178-CL-047, U00021856492] and one patient treated with mirabegron 50 mg [Patient No. 178-CL-046, 3018-1731] reported an SAE of acute retention of urine (LLT). No patients treated with tolterodine reported an SAE of urinary retention. There was 1/2131 (< 0.1%) mirabegron 50 mg patient (described above), 1/2142 (< 0.1%) placebo patient and there were 3/958 (0.3%) tolterodine patients who permanently discontinued study drug due to acute retention of urine.

In the EU/NA Long-term Controlled Population:

In the EU/NA Long-term Controlled Population, one or more urinary retention TEAEs was reported by 2/1632 (0.1%) mirabegron patients (mirabegron 50 mg: 1/812 [0.1%]; mirabegron 100 mg: 1/820 [0.1%]) and 3/812 (0.4%) tolterodine patients. One patient treated with mirabegron 100 mg ([Patient No. 178-CL-049, 2203-0481], a 59-year-old female who was postoperative for severe lumbar spinal stenosis) and one patient treated with tolterodine reported the TEAE (by LLT) of acute retention of urine. Another patient treated with tolterodine [Patient No. 178-CL-049, 3232-2147], a 65-year-old male also experienced the TEAE (by LLT) of acute retention of urine. No patients in the EU/NA Long-term Controlled Population reported an SAE of urinary retention.

Reviewer's Comment: Upon preliminary review, mirabegron does not appear to predispose to urinary retention as compared to placebo and tolterodine. Defining urinary retention as a change from baseline of >150mL did not demonstrate increased urinary retention with mirabegron. There also was no substantial difference in the incidence of urinary retention in patients who had or did not have BPH.

- Urolithiasis

While altered bladder storage of urine may be associated with the development of bladder stones, I am unaware of an association of upper urinary tract urolithiasis in association with altered bladder storage unless it is severe, leading to upper urinary tract anatomic changes and altered tubular function. There were no bladder calculi reported in the pivotal studies or in the long-term controlled study.

Increases in Serum Transaminases/Hepatotoxicity

Increases in Serum Transaminases/hepatotoxicity was identified at the November 14, 2007, End-of-Phase 2 (EOP2) meeting, as a potential concern. Based on preclinical studies in mice, rats, rabbits, dogs and monkeys, the liver has been identified as a target organ of concern.

- Mean changes in serum transaminases

In the Global OAB 12-week Phase 2/3 Population:

In the Global OAB 12-week Phase 2/3 Population, the mean increase from baseline to final visit for ALT was 0.3, 1.2, 0.5, 1.3, 0.8 and 0.9 U/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. The mean increase from baseline to final visit for AST was 0.3, 1.0, 0.3, 0.8, 1.1 and 0.3 U/L in the placebo, mirabegron 25 mg, mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg and tolterodine groups, respectively. The mean change from baseline to final visit in ALP (ranging from -2.1 U/L with mirabegron 200 mg to 2.9 U/L with placebo), bilirubin (ranging from -0.02 mcml/L with tolterodine to -0.42 mcml/L with mirabegron 50 mg) and GGT (-0.7 U/L with mirabegron 200 mg to 1.9 U/L with tolterodine) were generally similar across all treatment groups.

In the EU/NA Long-term Controlled Population:

In the EU/NA Long-term Controlled Population, the mean change from baseline to final visit for ALT, AST, ALP, bilirubin and GGT were similar across the mirabegron 50 mg, 100 mg and tolterodine treatment groups, with a similar pattern of change over time in ALT and AST (see Table 28). The mean change from baseline to final visit for GGT was actually higher in the tolterodine group compared with the mirabegron groups. The mean changes from baseline in all analytes were of small magnitude compared to the normal range of the analyte. Mean changes from baseline to final visit in ALT, AST, bilirubin, GGT and LDH were small and similar across all treatment groups, with a similar pattern of change in ALT and AST. There were no mean increases in serum bilirubin in any group.

Reviewer's Comment: The mean increases from baseline in serum AST and ALT in the Global 12-Week Phase 2/3 Population appear slightly greater for mirabegron compared to placebo overall, but these mean increases are small. This same finding was not observed in the EU/NA, Long-term Controlled Population. In fact, in that population, there was a slight mean increase in serum ALT in the tolterodine group compared to slight decreases in the mirabegron groups. This will be a review issue.

Table 28: Hepatic Chemistry Results, EU/NA Long-term Controlled Population

Laboratory Parameter (Units)	Mirabegron		Tolterodine
	50 mg n=812	100 mg n=820	ER 4 mg n=812
ALT(U/L)	Mean (SD) [n]		
Baseline	22.9 (10.94) [810]	22.1 (12.20) [820]	21.8 (10.45) [812]
ΔBaseline to Final Visit	-0.2 (10.58) [790]	-0.6 (12.42) [803]	0.1 (9.65) [791]
95% CI	(-1.0, 0.5)	(-1.4, 0.3)	(-0.6, 0.8)
AST(U/L)	Mean (SD) [n]		
Baseline	22.5 (7.55) [810]	22.0 (9.06) [820]	21.8 (7.18) [812]
ΔBaseline to Final Visit	-0.2 (8.07) [789]	-0.4 (9.06) [803]	-0.4 (6.45) [791]
95% CI	(-0.8, 0.4)	(-1.0, 0.2)	(-0.8, 0.1)
Bilirubin(mcmol/L)	Mean (SD) [n]		
Baseline	7.62 (3.955) [810]	7.72 (4.164) [820]	7.92 (4.130) [812]
ΔBaseline to Final Visit	0.10 (3.057) [790]	-0.15 (3.190) [803]	-0.23 (3.44) [791]
95% CI	(-0.11, 0.31)	(-0.37, 0.07)	(-0.47, 0.00)

Source: Table 51, SCS, page 109

- Outliers for hepatic chemistries

The following table serves to illustrate the frequency of outliers with regard to hepatic chemistries in the Global Phase 2/3 Population:

Table 29: Potentially Clinically Significant Hepatic Chemistry Abnormalities, Global Phase 2/3 Population

Laboratory Parameter (Units) n/n (%) of Patients	Criteria	Total Mirabegron (n=5863)	Total Placebo (n=2142)
ALT or AST (U/L)	>3 x ULN	57/5727 (1.0%)	11/2087 (0.5%)
	>5 x ULN	15/5727 (0.3%)	3/2087 (0.1%)
	>10 x ULN	5/5727 (0.1%)	1/2087 (<0.1%)
	>20 x ULN	1/5727 (<0.1%)	1/2087 (<0.1%)
ALT (U/L)	>3 x ULN	49/5727 (0.9%)	9/2087 (0.4%)
	>5 x ULN	12/5727 (0.2%)	2/2087 (0.1%)
	>10 x ULN	3/5727 (0.1%)	0/2087
	>20 x ULN	1/5727 (<0.1%)	0/2087
AST (U/L)	>3 x ULN	26/5727 (0.5%)	3/2087 (0.1%)
	>5 x ULN	7/5727 (0.1%)	2/2087 (0.1%)
	>10 x ULN	3/5727 (0.1%)	1/2087 (<0.1%)
	>20 x ULN	0/5727	1/2087 (<0.1%)
ALP (U/L)	>1.5 x ULN	30/5727 (0.5%)	9/2087 (0.4%)
Bilirubin(mcmol/L)	>1.5 x ULN	40/5727 (0.7%)	12/2087 (0.6%)
	>2 x ULN	9/5727 (0.2%)	3/2087 (0.1%)

Source: Table 52, SCS, page 112 and Table 7.3.2.1 ISS.

Reviewer's Comment: The incidences of ALT and AST outliers with elevations greater than 3 times normal and greater than 5 times normal appears modestly increased in the mirabegron groups compared to placebo. This will be a review issue.

In the Global Phase 2/3 Population, hepatic laboratory parameters were also assessed by criteria based on multiple laboratory parameters.

Overall, 1/5860 (< 0.1%) mirabegron patient [Patient No. 178-CL-049, 3353-1381] experienced a PCS (potentially clinically significant) hepatic chemistry laboratory abnormality of ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN on the same date; the results for this patient are the same when values within 3 days are considered. Two other mirabegron patients, [Patient No. 178-CL-045, J5405034-P00244] and [Patient No. 178-CL-049, 3353-1381], were identified as having 3 fold or more transaminase elevation combined with 2 fold or more bilirubin elevation, but in both cases, there were mitigating circumstances. In one of these patients [Patient No. 178-CL-045, P00244], the criteria were met in local laboratory analysis only and the local laboratory results are not included in the database. In the other patient, [Patient No. 178-CL-049, 3353-1381], concurrent increased ALP was observed and ongoing viral hepatitis was an alternate etiology.

Reviewer's Comment: Three patients with potentially clinical significant increases from baseline in serum transaminases coupled with at least 2-fold increases in serum bilirubin (Patient No. 178-CL-049, 3353-1381; Patient No. 178-CL-045, J5405034-P00244; and Patient No. 178-CL-049, 3353-1381) will be a review issue.

In the EU/NA Long-term Controlled Population, the frequency of PCS abnormalities in hepatic laboratory tests was low ($\leq 1.3\%$) and similar across treatment groups. Two patients that took mirabegron 100 mg and mirabegron 50 mg respectively, [Patient No. 178-CL-049, 3051-2649] and [Patient No. 178-CL-049, U00020446398], had ALT or AST > 10 x ULN. The incidence of Potentially Clinically Significant Hepatic Chemistry Abnormalities was similar to the 12-week Global Phase 2/3 Population. There were no patients in the EU/NA Long-term Controlled Population mirabegron 100 mg dose or in the tolterodine group who met any of the following criteria:

- ALT and/or AST > 3 x ULN and Total Bilirubin > 2x ULN and ALP < 2 x ULN on the same date
- ALT and/or AST > 3 x ULN and Total Bilirubin > 2X ULN and ALP < 2 x ULN within 3 days
- ALT and/or AST > 3 x ULN and Total Bilirubin > 1.5 x ULN on the same date
- ALT and/or AST > 3 x ULN and Total Bilirubin > 1.5 x ULN on the same date ALT and/or AST > 3 x ULN and Total Bilirubin > 1.5 x ULN within 3 days
- ALT and/or AST > 3 x ULN and Total Bilirubin > 2 x ULN on the same date
- ALT and/or AST > 3 x ULN and Total Bilirubin > 2 x ULN within 3 days

Reviewer's Comment: Two patients with greater than 10-fold increases from baseline serum transaminases (Patient No. 178-CL-049, 3051-264; and Patient No. 178-CL-049, U00020446398) will be a review issue.

In each of the six categories above, the incidence for the mirabegron 50 mg dose group was 1/812. I believe these all occurred in the same patient:

Patient No. 178-CL-049, 3353-1381, a 67 year-old man treated with mirabegron 50 mg, had 3 fold or more transaminase elevation combined with 2 fold or more bilirubin elevation, but had a history of chronic hepatitis B and alcohol abuse. ALT, AST and total bilirubin were elevated throughout the study as well as in the prior study (Study 178-CL-046, where he received tolterodine). The patient also experienced a mild TEAE of hepatic enzyme increased (day 36), considered by the investigator as mild and not related to the study drug. On day 185, the patient had AST of 120 U/L history of chronic hepatitis B and alcoholism was considered to be an alternate etiology.

The Sponsor concludes that in the Global Phase 2/3 Population, one or more hepatotoxicity TEAE was reported by 325/5863 (5.5%) mirabegron patients [Module 5.3.5.3 ISS Table 6.8.1.1]. The Japanese phase 2/3 studies had higher proportions of patients with hepatotoxic AE since any abnormal value representing at least a 20% worsening from baseline was required by protocol to be reported as an AE. Given that few patients experienced a PCS hepatic chemistry laboratory abnormality [Section 3.2.1.3.1], the higher frequency of hepatotoxic AE does not represent a greater hepatotoxic risk in this population.

In the Global OAB 12-week Phase 2/3 Population, one mirabegron 25 mg, one mirabegron 50 mg and one tolterodine patient, as well as 3 mirabegron 100 mg patients in the EU/NA Long-term Controlled Population, reported an SAE of hepatotoxicity. All recovered or are in the process of recovering.

Overall, SAE events have been rare and no cases of severe drug induced liver injury have been reported during the mirabegron program.

Reviewer's Comment: Upon preliminary review, the incidence of hepatic chemistry abnormalities with mirabegron appears low, but continues to be a review issue.

Endocrine and Metabolic Disorders

In animals, it has been shown that stimulation of beta 3-ARs prevents or corrects hyperglycemia. Based on this finding, the Sponsor studied mirabegron as a treatment for hyperglycemia due to diabetes mellitus. Although no significant effect on blood glucose was demonstrated in two 12-week proof-of-concept studies for treatment of diabetes mellitus, the potential risk of mirabegron on causing hypoglycemia was assessed.

- Study 178-CL-003 examined the effect of placebo and mirabegron administered in addition to diet and exercise for 12 weeks in the treatment of 59 patients with type 2 diabetes mellitus. Mirabegron was administered as an IR formulation given once daily in the AM with 3 escalating dose levels (60 mg, 130 mg, 200 mg). The primary endpoint of the study was the change from baseline in HbA1c. Fasting blood glucose values were measured throughout the study and showed no difference between the change from baseline to final visit in the mirabegron (0.34 mmol/L) and placebo (0.32 mmol/L) treatment groups. There were no reports of hypoglycemia in this study.

- Study 178-CL-004 examined the effect of placebo and mirabegron administered in addition to metformin, diet and exercise for 12 weeks in the treatment of 60 patients with type 2 diabetes mellitus. Mirabegron was administered as an IR formulation given once daily in the AM with 3 escalating dose levels (60 mg, 130 mg, 200 mg). Fasting blood glucose values were measured throughout the study and showed no difference between the change from baseline to final visit in the mirabegron + metformin (0.88 mmol/L) and placebo + metformin (0.87 mmol/L) treatment groups. There were no observations of hypoglycemic events in this study.
- In the 12-week Phase 2/3 Population, the mean changes for fasting blood glucose from baseline to final visit for placebo, mirabegron 25 mg, 50 mg, 100 mg, 200 mg and tolterodine ER 4 mg were 0, -0.002, 0.06, 0.07, 0.17 and 0.02 mmol/L respectively. The changes for HbA1c from baseline to final visit for placebo, mirabegron 25 mg, 50 mg, 100 mg, 200 mg and tolterodine ER 4 mg were 0.03, 0.06, 0.03, 0.01, N/A and 0 per cent respectively. Similar blood glucose changes were noted in the EU/NA Long-term Controlled Population. The incidence of hypoglycemia in the EU/NA 12-week Phase 3 population was 2/2736 (0.1%) versus 1/1380 (0.1%) and no patient reported hypoglycemia.
- In the EU/NA OAB 12-week Phase 3 Population, one or more hyperglycemia TEAE was reported by 25/2736 (0.9%) mirabegron, 13/1380 (0.9%) placebo and 3/495 (0.6%) tolterodine patients. In the EU/NA Long-term Controlled Population, one or more hyperglycemia TEAE was reported by 30/1632 (1.8%) mirabegron patients (mirabegron 50 mg: 16/812 [2.0%]; mirabegron 100 mg: 14/820 [1.7%]) and 13/812 (1.6%) tolterodine patients.

Reviewer's Comment: Upon preliminary review, it appears that mirabegron does not exert a clinically significant change on fasting blood glucose or HbA1c.

Based upon one SAE of hypothyroidism in the phase 2 program, a program-wide evaluation was conducted to assess the potential risk of thyroid dysregulation. The Sponsor concludes that an evaluation of mean, shift 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 TEAEs were reported in the Global OAB 12-week Phase 2/3 Population at a comparable frequency across treatment groups. Data from the clinical program support the thyroid function safety of mirabegron 50 mg in the treatment of OAB patients.

Hypersensitivity Reactions

Two cases of potential hypersensitivity reaction in the global mirabegron development program (an SAE of reported Stevens-Johnson syndrome in a phase 2 study [eventually classified as urticaria by an adjudication committee], and leukocytoclastic vasculitis in a phase 1 study) prompted a comprehensive program-wide evaluation of potential hypersensitivity events. The results of this evaluation are in Research Report: Mirabegron and Hypersensitivity submitted in this NDA submission.

Narratives for the two cases that prompted this evaluation are provided herein:

Patient No. 178-CL-045, P00244: This was a 74-year-old Japanese woman treated with mirabegron 100 mg, who was initially assessed by the investigator as having drug-induced

urticaria (not Stevens- Johnson syndrome) 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 non-serious event of WBC count decreased, concurrent with urticaria, with WBC count 2900 cells/ μ L on day 28 (5700 cells/ μ L at baseline). Study drug was withdrawn on day 30 and WBC count increased to 10,890 cells/ μ L with 4.5% atypical lymphocytes by day 37 [Hypersensitivity Appendix 4.2.1]. This patient also experienced elevated liver chemistry tests concurrent with the urticaria and leukopenia; laboratory results on day 28 revealed elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). 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 as Stevens-Johnson syndrome. However, the patient did not consent to allow the investigator access to her hospital 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 Stevens-Johnson syndrome. The Expert Committee also identified the leukopenia as a plausible, but not definite, part of the 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 by the patient on day 24 to day 26 just prior to the reaction's onset on day 26. 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.

Reviewer's Comment: The hypersensitivity reaction experienced by Patient No. 178-CL-045, P00244, and its relationship to mirabegron versus Kyufu Gold herbal medication, versus some other condition, will be a review issue.

Volunteer No. 178-CL-076, U00022981217: This 19-year-old woman treated with mirabegron 30 mg IV/100 mg (po) in a Phase 1 study, had findings suggestive of a hypersensitivity reaction. On study day 35, 4 days following the single dose of mirabegron 100 mg OCAS target release formulation, an SAE was reported by the investigator as a probable drug hypersensitivity vasculitis - delayed sensitivity reaction. However, the volunteer began experiencing symptoms associated with this hypersensitivity reaction approximately 4 days prior (study day 31) to the event. The volunteer presented to the emergency room with complaints of a skin rash that was described as pruritic and painful and was treated with methylprednisolone and diphenhydramine. The event was considered moderate in severity and possibly related to study drug. The volunteer also had an SAE of acute polyarticular arthritis concurrent with the probable drug hypersensitivity vasculitis, on study day 36. The study drug was permanently discontinued on day 31. At the last study visit, on day 45, the probable drug hypersensitivity vasculitis was reported as resolved. The Expert Committee identified the event as a definite hypersensitivity reaction characterized as cutaneous vasculitis. In addition, the Expert Committee identified polyarthritis as part of the hypersensitivity reaction that occurred concurrently with the cutaneous vasculitis.

Reviewer's Comment: The hypersensitivity reaction experienced by Patient No. 178-CL-076, U0002298121 (hypersensitivity vasculitis and polyarthritis), and its relationship to mirabegron will be a review issue.

These cases prompted Sponsor to conduct a broad search to capture potential hypersensitivity events in the mirabegron clinical database.

The Sponsor's conclusions from this evaluation are:

- Across all populations, the Expert Committee identified 2 plausible hypersensitivity reaction cases of immediate type. Both occurred in patients from the Global 12-week Phase 2/3 Population (1/2292 [$< 0.1\%$] placebo, 0/3012 mirabegron < 100 mg, 1/1667 [0.1%] mirabegron ≥ 100 mg and 0/1022 tolterodine patients) and included pruritus generalized in a mirabegron-treated patient and urticaria in a placebo-treated patient.
- Across all populations, the Expert Committee identified 38 subjects who experienced plausible hypersensitivity reactions of nonimmediate type, including 33 subjects with hypersensitivity reactions assessed as primarily cutaneous and 6 subjects with hypersensitivity reactions assessed as primarily noncutaneous. One subject experienced 2 nonimmediate hypersensitivity reactions – one categorized as primarily cutaneous (urticaria) and the other categorized as primarily noncutaneous (leukopenia).
- Across all populations, the Expert Committee identified 5 patients who experienced plausible hypersensitivity reaction of undetermined type: 3 patients from the Global 12-week Phase 2/3 Population (1/2292 [$< 0.1\%$] placebo, 0/3012 for mirabegron < 100 mg, 2/1667 [0.1%] for mirabegron ≥ 100 mg and 0/1022 for tolterodine patients) and 2 patients from EU/NA Long-term Controlled Population (0/812 mirabegron 50 mg, 1/820 [0.1%] mirabegron 100 mg and 1/812 [0.1%] tolterodine patients). None of these cases were identified as definite hypersensitivity reactions.
- 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 patients, but there was not a consistent pattern to establish an association of mirabegron with nonimmediate, primarily noncutaneous hypersensitivity reactions.
- Non-immediate, primarily cutaneous hypersensitivity reactions of urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, and lip and eyelid edema, occurred in mirabegron-treated patients 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 is clearly indicated

Reviewer's Comment: Hypersensitivity reactions have been reported in patients taking mirabegron. The relationship of these events to mirabegron and their severity will be review issues.

Glaucoma

Following the report of 2 SAEs of glaucoma in the mirabegron clinical studies, the Sponsor conducted a systematic evaluation of AEs reported as glaucoma, increased intraocular pressure, or glaucoma-type AE in all completed clinical studies. Twelve cases were retrieved using the glaucoma SMQ (narrow search) in the mirabegron clinical development program. An 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

Reviewer's comment: One of these patients had insufficient information to confirm or refute glaucoma but the Sponsor included the case "conservatively" as glaucoma

- 1 case was classified as nonglaucomatous, 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.

Reviewer's Comment: The specific events and issues associated with each of the 12 glaucoma AEs will be a review issue.

The percentage of patients with glaucoma events based on an expert panel assessment in the Global OAB 12-week Phase 2/3 Population was 0% (0/2142 patients; 95% CI: 0.00%, 0.17%) for placebo, < 0.1% (2/4414 patients; 95% CI: 0.01%, 0.16%) for mirabegron and 0% (0/958 patients; 95% CI: 0.00%, 0.38%) for tolterodine. In the EU/NA Long-term Controlled Population, the percentage of patients with glaucoma events based on the expert panel assessment was 0.1% (2/1632 patients; 95% CI: 0.01%, 0.44%) for mirabegron and 0.1% (1/812 patients; 95% CI: 0.00%, 0.68%) for tolterodine.

Subsequently, the Division requested that Sponsor conduct a dedicated study to assess the effect of mirabegron on intraocular (IOP). This was a randomized, double-blind, placebo-controlled, non-inferiority study. According to the Sponsor, the suprathreshold 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, based on the non-inferiority limit of 1.5 mm Hg. IOP data from day 10 were concordant with day 56. No subject discontinued the study due to an increased IOP. Clinically significant increases in baseline IOP measurements occurred rarely and only in placebo-treated patients. Visual acuity and biomicroscopy data were generally unremarkable in this study with no reported glaucoma-type AE.

Reviewer's Comment: The evidence from the double-blind, non-inferiority study does not appear to support an association between mirabegron and glaucoma. An Ophthalmology consultation from the Division of Transplant and Ophthalmology Products (DTOP) has been requested to evaluate the evidence.

Neoplasms

A difference in the number of adverse events in the Neoplasms category was observed between mirabegron and tolterodine in Study 049, also referred to as the EU/NA Long-term Controlled Population. There were 12 patients with adverse event reports in the Neoplasm category in the

mirabegron groups (1 in mirabegron 50 mg [1/812; 0.1%] and 11 in mirabegron 100 mg groups [11/820; 1.3%]). There were 4 patients with adverse event reports in the Neoplasm category among 812 patients in the tolterodine group (4/812; 0.5%).

Reviewer's Comment: The difference in the frequency of reporting of neoplasm AEs between mirabegron 100 mg and tolterodine is a review issue.

The Sponsor analyzed the frequency of reporting of Neoplasms by dividing the Study 049 study population into the following 3 groups: 1) subjects who took mirabegron **only** (n=1632), 2) subjects who took tolterodine **only** (n=444), and 3) subjects who took **both** mirabegron and tolterodine at some point in their clinical trial participation – either mirabegron first, then tolterodine (n=368) or tolterodine first then mirabegron (n=237).

Reviewer's Comment: The Sponsor's analysis of the Neoplasm AE by categorizing patients as recipients of mirabegron only, tolterodine only, or both mirabegron and tolterodine, requires additional consideration and will be a review issue.

The Sponsor conducted an overall analysis of the entire clinical experience for neoplasms. They also employed an adjudication committee to analyze each case generated from the clinical trial safety databases search. The following represents their conclusions regarding “new malignant events” among 2444 patients who participated in Study 049:

- The overall incidence rate of “new malignant events” in patients who received mirabegron (both mirabegron dose groups combined) was 0.74% (12 of 1632 patients). This includes patients who received mirabegron only (11/1395; 0.79%), and patients who received tolterodine in the previous, placebo-controlled Phase 3 study (Study 046) then mirabegron in Study 049; referred to as tolterodine/mirabegron (1/237; 0.42%).
- The overall incidence of “new malignant events” in patients who received tolterodine was 0.49% (4 of 812 patients). This includes patients who received tolterodine only (3/444; 0.68%) and patients who received mirabegron in the previous, placebo-controlled Phase 3 study (either Study 046 or 047), then tolterodine in Study 049; referred to as mirabegron/tolterodine (1/368; 0.27%).

Based on these data, the Sponsor states that the relative risk (RR) of “new malignant events” for the mirabegron-only group compared with the tolterodine-only group was 1.17 (95% CI: 0.31, 6.55). The RR of “new malignant events” for the total mirabegron group (mirabegron only and tolterodine/mirabegron groups) compared with the total tolterodine group (tolterodine only and mirabegron/tolterodine groups) was 1.50 (95% CI: 0.45, 6.38).

An analysis of the incidence rate by “patient-years at risk” demonstrated similar results to the analysis based upon frequency of patients.

Reviewer's Comments:

1. *The Sponsor's analysis of “new malignant events” requires careful consideration and will be a review issue.*
2. *The Sponsor's analysis of risk by patient-years requires further consideration and will be a review issue.*

A total of 21 “new malignant events” were reported in the 16 patients in this analysis. These 21 events included tumors from 7 different organs of origin. The Adjudication Committee provided

their opinion that 11 of 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 [transitional 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]).

Reviewer’s Comment: The Adjudication Committee’s determinations regarding drug-relatedness will be a review issue.

Neoplasms were reported in some patients in safety populations other than the EU/NA Long-term Controlled Population. For example, SAEs within the SOC of neoplasms benign, malignant and unspecified in the Global OAB 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. The reported SAEs were heterogeneous and represented benign as well as malignant events, generally reflecting the most prevalent malignancies in the US and Europe.

The Sponsor notes that the observed numerical imbalance of “new malignant events” in the Global Phase 2/3 Population was due in large part, to events reported in the Global OAB 12-week Phase 2/3 Population. Review of the individual 12-week study data reveals an observed numerical imbalance of adjudicated new malignancies in only one study (Study 178-CL- 047), which was not replicated in the other 5 studies included in the Global OAB 12-week Population. Based on the adjudicated results (Sponsor’s Neoplasm Adjudication Committee), the RR (mirabegron vs pooled comparator treatments) for patients with new malignant events was 2.45 (95% CI: 0.51, 11.78) in the Global OAB 12-week Phase 2/3 Population and 1.83 (95% CI: 0.74, 4.55) in the Global Phase 2/3 Population.

Reviewer’s Comment: The observed imbalance in new malignant events in the Global Phase 2/3 Population, and the effect of an imbalance of such events in Study 047 will be a review issue.

With respect to the neoplasms arising in the Global OAB Phase 2/3 Population, Study 178-CL-047, individual brief case narratives are provided herein:

- **Subject U00016297440 mirabegron 50 mg: Prostate Cancer:** During a routine prostate examination on Day 7, a prostate nodule was detected on routine physical exam that eventually was diagnosed as prostate cancer on Day 21. There is no PSA level noted in the narrative.
- **Subject U00016176141 mirabegron 50 mg: Prostate Cancer:** On Day -15, asymmetric induration of the right prostatic lobe was noted on examination. On Day 90, induration “suggesting tumor” was noted by the investigator and the PSA was 2.3 ng/mL. The subject was noted to have a PSA of 10.50 ng/ml on Day -309.
- **Subject U00021787330 placebo: Malignant Lung Neoplasm.**
- **Subject U00016176141 mirabegron 100 mg: Metastatic Colon Cancer, Bladder Cancer, Death:** On Day 3 and Day 28 the patient experienced episodes of hematuria. The patient had a past history of stage IV colon cancer and colon resection. She was

ultimately found to have colon cancer with metastases to the bladder (bladder tumor). She ultimately expired from her colon cancer.

- **Subject U00021866960 mirabegron 100 mg: Recurrent Lung Cancer:** On Day 21, a recurrence of cancerous growth on the right lung was reported. The patient had a medical history of a melanoma removed from the left chest area, cancerous tumor on right lung, and surgery to remove tumor on right lung.
- **Subject U00021897244 mirabegron 100 mg: Malignant melanoma and sentinel lymph node metastases:** This patient had a history of actinic keratosis and had a biopsy-confirmed diagnosis of malignant melanoma on day 20. Lymph node metastases were identified on lymphoscintigraphy on Day 47.

Reviewer’s Comment: All of the above lesions appear to be pre-existing conditions. It is unlikely that the disproportion of neoplasm adverse events in the 12-week studies represents a signal for neoplasia related to mirabegron, in my opinion.

The Sponsor states the rates of the most frequent malignancies reported in mirabegron-treated patients did not deviate from those expected in an age adjusted population.

The following is a table of the 11 patients with serious adverse events (SEAs) of neoplasms – out of the total of 16 patients with neoplasm AEs in Study 049.

Table 30: Study 178-CL-049 Serious Adverse Events of Neoplasms

Patient No/Age/Race/Sex/Country	MedDRA (v9.1) Preferred Term	Onset/Stop Day (Last Dose Day)	Treatment in Previous Study (046/047/Naïve)	Additional Information: Adjudication
Mirabegron 50 mg				
2179-6744 54/White/Femal/ US	Endometrial Cancer Stage I	315/350 (364)	Placebo (047)	Heavy Vaginal Bleeding X1yr: “Possible Growth of preexisting neoplasm.”
Mirabegron 100 mg				
1597-7875 61/White/Female/ US	Breast Cancer	86/Ongoing (294)	Mirabegron 100 mg (047)	Lesion noted Day 19 of Study
1651-8100 70/White/Male/ US	Prostate Cancer	54/Ongoing (58)	Mirabegron 50 mg (047)	Day 28 PSA 5.4 Day -162 PSA 3.49
2262-0172 52/White/Female/ Canada	Endometrial Cancer	139/216 (166)	Naive	Postmeopausal vaginal bleeding noted Day 83: “Possibly related to study drug but unlikely”

3016-1796 48/White/ Female/Germany	Hypopharynx Fibroma	329/332 (364)	Tolterodine SR 4 mg (046)	“Not related to either study drug and no prior evidence”
3016-1952 61/White/Female/ Germany	Lung Neoplasm Malignant	126/Ongoing (175)	Mirabegron 50 mg (046)	Presenting symptoms Day 97: “No evidence pre- existing, nor for study drug to growth and presentation”
3022-0128 69/White/Male/ Germany	Prostate Cancer	49/85 (82)	Naive	PSA 6.6 Day-14: “Not related to study drug”
3025-2505 64/White/Male/ Germany	Pancreatic Carcinoma	323/376 (323)	Tolterodine SR 4 mg (046)	Initial symptoms Day 295: “possible but unlikely related role in tumor stimulation cannot be R/O”
3032-2166 69/White/Male/ Germany	Thyroid Neoplasm	263/269 (364)	Mirabegron 100 mg (046)	Path-no indication of malignant process: Worsening of lesion predated 046.
3034-2276 71/White/Female/ Germany	Breast Cancer	92 E (362)	Placebo (046)	Lesion on mammogram Day 92: “Too little time to cause lesion to be visible on mammogram”
3062-2853 58/White/Male/ France	Transitional Cell Carcinoma (bladder)	309/ongoing (308)	Placebo (046)	WBC & RBC (Day 30) in U/A for 4 mos: prior polypectomy, “stimulation of tumor growth by study drug cannot be R/O.”
3235-2623 74/White/Female/ Sweden	Lung Neoplasm Malignant	53/ongoing (55)	Placebo (046)	Bronchitis noted Day-18: “Evidence for pre-existing”
Tolterodine ER 4 mg				
3013-0077	Breast Cancer	203/ongoing	Naive	Dx routine

51/White/Female/ Germany		(370)		mammography: “Possibility for tumor stimulation but no evidence of such.”
3020-0298 60/White/female/ Germany	Breast Cancer Benign Lung Neoplasm	293/ongoing/(364) 300/ ongoing/ (364)	Naive	No prior mammogram
3020-0298 40/White/Female/ France	Uterine Leiomyoma	300/353 (364)	Tolterodine SR 4 mg (046)	Menorrhagia since 2007: “No evidence of enlargement of leiomyoma”
3235-1509 64/White/Female/ Sweden	Endometrial Cancer	296/ongoing/ (317)	Tolterodine SR 4 mg (046)	Post menopausal vaginal bleeding: “Bleeding could represent stimulation by study drug.”

Source: Table 24, 178-CL-049 Study Report, page 118.

Reviewer’s Comment: Whether any of these neoplastic conditions were pre-existing, and whether differences between groups in frequencies of reporting of neoplasm AEs remains after excluding certain cases, will be review issues.

3.5.5 Preliminary safety and tolerability conclusions

Mirabegron is a new molecular entity which appears to be reasonably well tolerated by OAB patients. The extent of patient exposure to mirabegron in clinical studies is adequate to analyze safety. Several safety-related review issues are noted in this Clinical filing review:

- Cardiovascular safety of mirabegron will require additional review:
 - Mirabegron appears to have a modest effect on increasing both pulse and blood pressure.
 - Mirabegron may prolong the corrected QT interval at supratherapeutic doses in females,
 - Mirabegron may also be associated with clinical adverse events of tachycardia, palpitations, and a small number of cases of atrial fibrillation.
 - Clinical adverse events coded as “hypertension”, especially those occurring soon after treatment, need to be individually reviewed.
 - One patient in the 50 mg dose group of 178-CL-49 was administratively categorized under the MedDRA heading “QT prolongation/torsades.” This patient had cardiac arrest, ventricular fibrillation and ventricular tachycardia. The patient did not have torsades or QT prolongation.
- The frequency of increased hepatic chemistry laboratories in clinical trials appears increased with mirabegron and this will require additional review. The frequency of

increased serum transaminases; and rarely, serum bilirubin, will be a review issue. The individual clinical AE cases coded as “hepatotoxicity” will be reviewed.

- Hypersensitivity reactions. Each of these cases will require individual review.
- Sporadic clinical AEs of “glaucoma” and the potential for mirabegron to increase intraocular pressure are review issues.
- Whether there is a higher incidence of clinical AEs of neoplasm or “new malignant events” in patients receiving mirabegron versus those receiving tolterodine in Study 049, or placebo in short-term studies, is a review issue.
- 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 and long-term controlled studies than without baseline use of alpha 1-AR antagonists. Overall, the frequency of reporting of clinical adverse events codes as “hypertension” was generally higher among users of alpha 1-AR antagonists compared to nonusers of alpha 1-AR antagonists. These findings applied to mirabegron, placebo and tolterodine groups. This is a review issue.
- Frequency of reporting of TEAE was generally higher in female patients compared with male patients across treatment groups. Clinical AE reports coded as “hypertension, one of the most frequent TEAE reported in the mirabegron clinical studies, was generally observed more in male patients than in female patients. These will be review issues.
- Consultative reviews of selected safety issue have been requested. These include:
 - A consult to the Division of Transplant and Ophthalmology Products (DTOP) to assess the sporadic cases of “glaucoma” and the results of a placebo-controlled, intraocular pressure study.
 - A consult to the Division of Cardiovascular and Renal Products (DCRP) to assess the potential for mirabegron to increase blood pressure and the clinical significance of such an increase, if any.
 - A consult to the Interdisciplinary Review Team-QT (IRT-QT) to assess the potential for mirabegron to prolong the corrected QT interval.

4 Other considerations of Filing Review

4.1 Review of Financial Disclosure Documents

Form FDA 3454, dated July 26, 2011, and signed by Stephen Knowles, Vice President, Finance and Procurement, Astellas Pharma Global Development, Inc., was submitted. Financial disclosure documents (Form 3455) were submitted for clinical investigator [REDACTED] (b) (6) an investigator in the 178-CL-047 and 178-CL-049 clinical studies, indicated receiving significant payments of other sorts (as defined in 21 CFR 54.2(f)) from Astellas, as related to his national consulting role in regards to VESicare and other honoraria. Since these significant payments of other sorts are related to another drug, and this is not related to the research he conducted as an investigator in the mirabegron clinical studies, it is not believed that these payments/honoraria will bias [REDACTED] (b) (6) data for this NDA.

A total of 189 investigators from 189 sites in Study 178-CL-046, 128 investigators from 128 sites in Study 178-CL-047, and 147 investigators from 147 sites in Study 178-CL-074 were enrolled. The long-term safety study 178-CL-049 was conducted at 306 sites. Only one investigator had

disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.2(a)], proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product [21 CFR 54.2(b)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.2(f)]. There was no disclosed .missing financial disclosure information for investigators.

4.2 Labeling

The proposed label complies with the basic requirements of the Physician Labeling Rule (PLR). Upon preliminary review, the proposed draft label includes the following key clinically relevant sections:

-
-
-
-
-



4.3 Consults

In addition to the safety-related consults mentioned previously in this review, the following standard consultations will be made for this NDA:

a. Pediatrics

The Sponsor is requesting a waiver from the requirement to conduct clinical studies of mirabegron in pediatric patients < 5 years of age. This request is based on the general understanding that OAB, the indication being sought, is not a condition in infants or young children who are not yet bladder trained. The Sponsor is also requesting a deferral for conducting clinical studies of mirabegron in pediatric patients ≥ 5 years of age. These requests are reasonable and acceptable to the Clinical reviewers; however, the Sponsor’s request will need to go before the Pediatric Review Committee (PeRC) as per standard procedures.

b. Division of Scientific Investigations (DSI) Audit

Routine DSI audit of 5 to 7 large clinical study investigative sites is recommended, given that this is a new molecular entity. The clinical sites have already been discussed with DSI, and a formal consult will be generated.

c. Division of Medication Error Prevention and Assessment (DMEPA) in the Office of Surveillance and Epidemiology (OSE)

The Sponsor's proposed tradename (b) (4) was denied by DMEPA on July 19, 2011 based upon look-alike risks to other products. The Sponsor was notified and a new tradename will be proposed and conveyed to DMEPA for their review. DMEPA will also be asked to review the package insert and container/carton labeling.

d. Patient Labeling Team in the Division of Medical Policy Program

The Patient Labeling Team in to review the Patient Package Insert for content and label comprehension.

4.5 Other review disciplines

A 45-Day NDA Filing meeting was held on October 21, 2011. Each review discipline presented on the contents of their sections and any review issues noted at filing. Most of the discipline-specific filing reviews are pending completion. The reader is referred to the individual discipline-specific filing reviews in DARRTS. At this time, there are no specific issues that require mention here.

5 Summary of Initial Clinical Review/Conclusion

Efficacy

A preliminary review of the efficacy data from Studies 046 and 047 appears to support statistically significant improvements in baseline compared to placebo in incontinence episode frequency, urinary frequency, and average volume voided per urination in OAB patients. Mirabegron also appears to have at least a comparable effect to tolterodine. The efficacy in OAB appears to be maintained for up to 1 year in Study 049.

Safety

Mirabegron is a new molecular entity which appears to be reasonably well tolerated by OAB patients. The extent of patient exposure to mirabegron in clinical studies is adequate to assess safety. Several safety-related review issues were noted in the Clinical filing review:

- Cardiovascular safety of mirabegron will require additional review:
 - Mirabegron appears to have a modest effect on increasing both pulse and blood pressure.
 - Mirabegron may prolong the corrected QT interval at supratherapeutic doses in females,
 - Mirabegron may also be associated with clinical adverse events of tachycardia, palpitations, and a small number of cases of atrial fibrillation.
 - Clinical adverse events coded as "hypertension", especially those occurring soon after treatment, need to be individually reviewed.

- The frequency of increased hepatic chemistry laboratories in clinical trials appears increased with mirabegron and this will require additional review. The individual clinical AE cases coded as “hepatotoxicity” will be reviewed.
- Mirabegron appears to be associated with rare hypersensitivity reactions. Each of these cases will require individual review.
- There have been sporadic clinical AE reports of “glaucoma” in mirabegron clinical trials. The Sponsor purports that a specially designed, placebo-controlled, intraocular pressure (IOP) study reveals no adverse effect of mirabegron on IOP. The potential for mirabegron to increase intraocular pressure is a review issue.
- Whether there is a higher incidence of clinical AEs of neoplasm or “new malignant events” in patients receiving mirabegron versus those receiving tolterodine in Study 049, or placebo in short-term studies, is a review issue.

Consultative reviews of selected safety issue have been requested. These include:

- A consult to the Division of Transplant and Ophthalmology Products (DTOP) to assess the sporadic cases of “glaucoma” and the results of a placebo-controlled, intraocular pressure study.
- A consult to the Division of Cardiovascular and Renal Products (DCRP) to assess the potential for mirabegron to increase blood pressure and the clinical significance of such an increase, if any.
- A consult to the Interdisciplinary Review Team-QT (IRT-QT) to assess the potential for mirabegron to prolong the corrected QT interval.

Conclusion

From a clinical perspective, the NDA is fileable. The following section contains Clinical review issues noted at filing that should be conveyed to Sponsor as part of the 74-Day Letter.

Recommended Regulatory Action: The following **Clinical** review issues that have been noted at filing should be conveyed to the sponsor in the 74 Day letter.

Efficacy

1. A difference in efficacy between older (≥ 65 years) and younger (< 65 years) patients was observed in Study 178-CL-046.

Safety

1. The role of mirabegron in the deaths of two patients: Patient Number 1530-6120 (multi-system organ failure) and Patient Number 3034-2380 (cardiac failure) in Study 178-CL-049 is unclear.
2. Regarding serious adverse events (SAEs):
 - a. In the EU/NA, 12-Week, Phase 3 Population:
 - i. A small difference was observed in incidence of atrial fibrillation SAEs between mirabegron and placebo.

- ii. Three urolithiasis SAEs were reported in the mirabegron group versus none in placebo.
 - iii. There appears to be a difference between mirabegron and placebo in total number of infection SAEs when a variety of different infections, each reported by 1 patient, are added together.
 - iv. There appears to be a difference between mirabegron and placebo in total number of neoplasm SAEs when a variety of different tumors, each reported by 1 patient, are added together. The relationship of these events to mirabegron in short-term (12-week) studies is unclear.
 - v. There are several injury SAEs in the mirabegron group versus none with placebo. Factors that may have contributed to these injuries (e.g. fatigue) will be considered during our case-by-case review.
- b. In the EU/NA Long-term Controlled Population:
- i. A higher incidence of atrial fibrillation SAEs was observed in the mirabegron group compared to the tolterodine group.
 - ii. A greater number of SAEs reported as “liver function test abnormalities” was observed in the mirabegron group (n=3) compared to the tolterodine group (n=1).
 - iii. A higher incidence of SAEs reported as “neoplasms” was observed in the mirabegron group (1.3%) compared to the tolterodine group (0.5%).
 - iv. A higher incidence of SAES reported as Musculoskeletal and Connective Tissue Disorders was observed in the mirabegron group compared to the tolterodine group.
3. Regarding discontinuations due to adverse events:
- a. In the EU/NA, 12-Week, Phase 3 Population:
- i. The incidences of discontinuations due to liver function test abnormalities and “hypertension” were higher in the mirabegron group compared to the placebo group. There are also two reports of “hypertensive crisis” leading to discontinuation.
 - ii. The incidence of discontinuation due to Skin and Subcutaneous adverse events was higher in the mirabegron group compared to placebo. Although no skin-related adverse event was reported in greater than 1 patient, there were multiple, single adverse event terms (n=5) reported, possibly indicative of an allergic or hypersensitivity phenomenon.
 - iii. “Hypertension” leading to study discontinuation was reported in 6 mirabegron subjects versus 2 placebo subjects.
- b. In the EU/NA Long-term Controlled Population:
- i. Fatigue was reported as a reason for discontinuation in 4 mirabegron subjects compared to 1 tolterodine subject.

- ii. Palpitations and tachycardia were reported as reasons for discontinuation in 0.6% and 1.0 % of mirabegron patients, respectively.
- 4. Regarding laboratory abnormalities:
 - a. Patient Number 2037-0516 in Study 178-CL-049 developed hemolytic anemia and thrombocytopenia as part of an apparent hypersensitivity reaction on Day 183. The role of mirabegron in this event is unclear.
 - b. There is a potential effect of mirabegron on interpreting urine dipstick protein analysis.
- 5. Regarding vital signs:
 - a. At a dose of 50 mg once daily, mirabegron appears to increase mean pulse rate by approximately 1-2 beats per minute over placebo. The increase in pulse rate secondary to mirabegron appears to be greater in women compared to men, as well as in younger compared to older patients.
 - b. At a dose of 50 mg once daily, mirabegron appears to increase mean blood pressure by approximately 1 mm Hg over placebo.
- 6. Regarding electrocardiograms (ECGs):
 - a. An increase in mean QTc interval was observed in female subjects dosed with mirabegron 200 mg.
 - b. A higher incidence of outliers with QTcF > 450 msec was observed in patients receiving mirabegron compared to placebo in 12-week studies.
 - c. Higher incidences of outliers with QTcF > 450 msec were observed in females compared to males, and in elderly (≥ 65 years) compared to non-elderly (< 65 years) patients in 12-week studies.
- 7. Regarding intrinsic and extrinsic factors that may affect safety:
 - a. In the Global OAB 12-Week Population, the incidence of overall adverse events was generally higher in female patients compared to male patients across treatment groups.
 - b. In the EU/NA OAB 12-week Population, the incidence of “hypertension” reported as an adverse event was higher in males than in females across treatment groups.
 - c. In the EU/NA OAB 12-Week population, the incidence of SAEs and discontinuations due to adverse events was generally higher in patients who were using alpha-1 adrenergic antagonists (alpha-1 blockers) at baseline compared to those not using alpha-1 blockers at baseline.
- 8. Regarding special safety issues:
 - a. Cardiovascular safety
 - i. The increases in blood pressure and pulse related to mirabegron, and the clinical significance of these increase, are under review.

- ii. In the EU/NA 12-Week OAB Population, the incidence of adverse events of “hypertension” leading to discontinuation was higher in the mirabegron group (all doses) (0.4%), compared to placebo (0.2%) and compared to tolterodine (0.2%).
 - iii. The degree of QT prolongation associated with mirabegron is under review.
 - iv. There was a single case of cardiac arrest with ventricular tachycardia and ventricular fibrillation in a mirabegron-treated patient in Study 178-CL-049.
 - v. Mirabegron appears to be associated with an increased risk of tachycardia as compared to placebo and tolterodine. Adverse events related to rapid pulse rate (e.g., cardiac arrhythmia, sinus tachycardia) are under review.
 - vi. The independent role of mirabegron in atrial fibrillation is under review.
- b. Urinary tract disorders
 - i. There appears to be an association of urinary tract infection (UTI) with use of mirabegron.
- c. Liver function test abnormalities
 - i. The mean increases from baseline in serum AST and ALT in the Global 12-Week Phase 2/3 Population are slightly greater for mirabegron compared to placebo.
 - ii. Patient Number 3353-1381 in Study 178-CL-049 experienced serum ALT and/or AST concentrations > 3 x upper limit of normal (ULN) and serum total bilirubin > 2 x ULN, with serum alkaline phosphatase (ALP) < 2 x ULN on the same date. This case, which appears to meet Hy’s Law, is under review.
 - iii. One other patient (Patient Number J5405034-P00244 in Study 178-CL-045) experienced potentially clinically significant increases from baseline in serum transaminases coupled with at least 2-fold increases in serum bilirubin.
 - iv. Two mirabegron patients experienced greater than 10-fold increases from baseline in serum transaminases (Patient Numbers 3051-264 and U00020446398 in Study 178-CL-049).
- d. Hypersensitivity reactions
 - i. Hypersensitivity reactions have been reported in patients taking mirabegron. The relationship of these events to mirabegron and their severity are under review.
 - ii. The severe hypersensitivity reaction experienced by Patient Number P00244 in Study 178-CL-045, and its relationship to mirabegron versus Kyufu Gold herbal medication, versus some other condition, is under review.
 - iii. The severe hypersensitivity reaction experienced by Patient Number U0002298121 in Study 178-CL-076 (hypersensitivity vasculitis and polyarthritis), and its relationship to mirabegron, is under review.

- e. Glaucoma/Increased intraocular pressure (IOP)
 - i. All clinical adverse event reports of glaucoma and increased IOP, as well as data from the dedicated, placebo-controlled, non-inferiority intraocular pressure study are under review.

- f. Neoplasms
 - i. There were 12 patients with adverse event reports in the Neoplasm category in the mirabegron groups in Study 178-CL-049 (1 in mirabegron 50 mg [1/812; 0.1%] and 11 in mirabegron 100 mg groups [11/820; 1.3%]). In comparison, there were 4 patients with adverse event reports in the Neoplasm category among 812 patients in the tolterodine group (4/812; 0.5%).

 - ii. The analysis of incidences of Neoplasm AEs by re-categorizing patients to mirabegron only, tolterodine only, or both mirabegron and tolterodine requires further consideration and is under review.

 - iii. The analysis of Neoplasm AEs by re-categorizing the events as “new malignant events” requires further consideration and is under review.

 - iv. The analysis of incidences of Neoplasm AEs by patient-years of exposure requires further consideration and is under review.

 - v. The Adjudication Committee’s determinations regarding drug-relatedness for each new malignant event is under review.

 - vi. The observed imbalance in new malignant events between mirabegron and placebo in the Global Phase 2/3 Population, and the effect of an imbalance of such events in short term studies such as 178-CL-047, is under review.

 - vii. Whether any of the Neoplasm AEs reflect pre-existing conditions, and whether differences between treatment groups in incidences of Neoplasm AEs remain after excluding certain cases, requires further consideration.

Appendix A: GRMP Clinical Reviewer Filing Checklist

NDA Number: 22-204

Applicant: Astellas

Stamp Date: 8/29/2011

Drug Name: To be determined

NDA Type: standard, original application

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: KMD-3213-US021-99 Study Title: A Pilot, Phase II, Placebo-Controlled, Double-Blind Study of KMD-3213 in Patients with the Signs and Symptoms of Benign Prostatic Hyperplasia (BPH) Sample Size: 264 Arms: 3 Location in submission: Module 5 – 5.3.5.1	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study#1: OG05009 Indication: OAB with urgency, frequency, and incontinence				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor requests waiver from requirement to conduct clinical studies in pediatric patients < 5 years of age.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

For a complete list of Clinical review issues noted at filing, the reader is referred to pages 81-85 of the Clinical Filing Review.

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

A R WIEDERHORN
11/16/2011

MARK S HIRSCH
11/16/2011
I concur.