Background Document for Meeting of Advisory Committee for Reproductive Health Drugs
April 5th, 2012

NDA 202611
Mirabegron Tablets
Astellas Pharma Global Development

Proposed Indication:
"Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency."

Dosing Regimen:
50 mg once daily without regard to food

Prepared by the Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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CLINICAL: EFFICACY AND SAFETY

Division of Reproductive and Urologic Products

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 202611 to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

EXECUTIVE SUMMARY

Efficacy Summary

The efficacy analyses included individual study and pooled data from three pivotal Phase 3 Studies 178-CL-046, 178-CL-047 and 178-CL-074). Efficacy was based on two co-primary efficacy endpoints: 1) the change from baseline to endpoint in the mean number of incontinence episodes per 24 hours as compared to placebo and 2) the mean change from baseline to endpoint in the mean number of micturitions per 24 hours as compared to placebo. Not all subjects had incontinence at baseline; therefore, the Full Analysis Set-Incontinence (FAS-I) includes only those subjects with incontinence at baseline, while the Full Analysis Set (FAS) includes all subjects.

For the 50 mg mirabegron tablet, the primary efficacy analysis demonstrated:

- ***Treatment with mirabegron 50 mg in the pooled efficacy analysis resulted in a reduction of incontinence episodes per 24 hours as compared to placebo of -0.40 ($p<0.001$ corrected for multiplicity).***
- ***Treatment with mirabegron 50 mg in the pooled efficacy analysis resulted in a reduction of micturitions per 24 hours as compared to placebo of -0.75 ($p<0.001$ corrected for multiplicity).***

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.

Secondary efficacy endpoints were evaluated including:

- ***Change from baseline to endpoint in mean voided volume in the pooled primary studies were also analyzed. These secondary endpoints were expressed as adjusted difference versus placebo. For mirabegron 50 mg, the change from baseline in mean voided volume was 11.9 cc ($p<0.001$ adjusted for multiplicity). Mirabegron 25 mg resulted in a mean change from placebo of 4.6 cc (p 0.15) which was not statistically significant.***

- ***At 4 weeks, a significantly decreased number of incontinence episodes for 24 hours were reported for mirabegron 50 mg as compared to placebo as well as a significantly decreased number of micturitions for 24 hours as compared to placebo.***

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.

Subpopulation efficacy analyses of clinical interest included:

- ***Gender: 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 subjects. A larger reduction versus placebo in mean number of incontinence episodes was observed in female subjects compared to male subjects. This could reflect a lower baseline level of incontinence in males, overlapping symptomatology with male co-morbid conditions (e.g., benign prostate hypertrophy), increased mirabegron exposure in females, or some combination of all 3 factors.***

- ***Age: Mirabegron 50 mg resulted in 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 (-0.22) as compared to 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 be improved efficacy in the over 65 year age group, compared to the under 65 years group, but this difference did not reach statistical significance. It does appear that overall, there is increased efficacy in subjects > 65 years of age as compared to subjects <65 years of age.***

- ***Body Mass Index (BMI) and Race: The interaction by subgroup based on body mass index (BMI) did not reach significant levels (p <0.05) for any BMI subgroup. There were too few subjects in categories other than White to allow further exploratory analysis.***

- ***Diabetics and subjects taking beta-blockers: Efficacy results were comparable to results in the general OAB study population.***

- ***Concomitant alpha-blocker use: Mirabegron 50 mg reduced the daily incidence of incontinence episodes similarly to the reduction in the overall study population. Results imply that the numbers of subjects using alpha-blockers was too small to draw meaningful conclusions.***

- ***Concomitant benign prostatic hyperplasia (BPH): Mirabegron 50 and 100 mg was not effective in decreasing the mean number of incontinence episodes in men with concomitant BPH. The 50 mg mirabegron dose only modestly decreased micturition episodes in men with BPH. There are too few men with BPH however, to draw meaningful conclusions.***

- ***Concomitant diuretic use: Efficacy of both mirabegron 50 mg and 100 mg was improved compared to subjects not on diuretics and exceeded the***

efficacy results in the overall study population for the primary efficacy endpoints.

After analysis, both mirabegron 50 mg and 25 mg showed statistically significant reductions in the number of incontinence episodes per 24 hours as compared to placebo and also in the number of micturitions per 24 hours as compared to placebo. As previously stated, the 100 mg dose is not under consideration for marketing approval. Finally, direct comparison of efficacy of mirabegron to tolterodine was not a primary objective of this application, and only very limited conclusions on efficacy comparisons can be drawn.

Safety Summary

The safety data from this NDA submission raise concerns related to the effect of mirabegron on heart rate, blood pressure, and liver function. In addition, there have been reports of hypersensitivity reactions, urinary tract-related adverse events (UTI and renal colic), and a variety of neoplasms in subjects in the clinical trials. Finally, concerns related to reports of glaucoma and increases in intraocular pressure were addressed through a dedicated intraocular pressure study.

The overview in this section is intended as a brief summary of the vast safety information contained in the NDA.

The studies performed were considered adequate to assess the safety of mirabegron used once a day for the treatment of OAB. In the pivotal and additional analysis sets supporting the OAB indication:

- ***There were a total of 8752 subjects in Phase 2/3 studies and 1800 volunteers in Phase 1 studies of which 7325 received mirabegron.***
- ***The Phase 2/3 Population receiving the to-be-marketed formulation formed the primary safety database. This database included a total of 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.***
- ***In the long-term controlled population study (consisting of subjects from Study 178-CL-049), 812 subjects were exposed to mirabegron 50 mg, 820 subjects were exposed to mirabegron 100 mg (of the total 1632, 901 subjects were re-exposures) and 812 subjects received tolterodine ER 4 mg active comparator.***
- ***Other studies included in the safety database:***
    - ***Phase 2 studies of either short duration (2-4 weeks) or were for a special purpose (a 12-week study in BPH subjects). 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.***

- *A Japanese long-term uncontrolled population, 153 subjects received mirabegron 50 mg and 50 subjects received mirabegron 100 mg as highest dose in this titrated study.*

- *A Global Phase 2/3 population, in subjects with continuous mirabegron exposure (n=5863), 4191 received mirabegron for ≥84 days, 1572 received mirabegron for ≥182 days and 622 subjects received mirabegron for ≥365 days.*
- *A Global Phase 2/3 population, 2458 subjects received mirabegron for a duration between 84 and 181 days, 875 subjects received mirabegron for a duration of 274-364 days and 603 subjects received mirabegron for ≥365 days.*

Demographics: Subjects 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 subjects were ≥ 65 years of age and approximately 12% of subjects were ≥ 75 years of age across the treatment groups

Deaths: In the entire mirabegron development program, there were 11 deaths, none of which appear directly related to treatment with mirabegron. There were 2 deaths in ongoing Study 178- CL-090 (one sudden death on blinded treatment and one death that occurred prior to randomization, a chemical poisoning). Nine deaths occurred in subjects participating in completed trials (5 subjects treated with mirabegron, one treated with placebo and 3 treated with tolterodine). Of the five deaths occurring in subjects treated with mirabegron: one subject 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.

Serious adverse events (non-fatal): In the overall mirabegron program, non-fatal serious adverse events were infrequent. Based on the demonstrated effects of mirabegron on blood pressure and pulse, the SAEs of greatest interest are atrial fibrillation and chest pain.

- ***In the OAB 12-week Phase 3 Population, one or more SAEs was reported for 62/2736 (2.3%) mirabegron, 29/1380 (2.1%) placebo, and 11/495 (2.2%) tolterodine subjects, with no apparent mirabegron dose response.***
- ***In the total mirabegron global safety database, the most common SAEs 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 subjects and not in placebo subjects, and possibly related to mirabegron, are listed in the body of this report.***

Treatment emergent adverse events (TEAEs list by preferred term [PT]) in subjects using mirabegron leading to permanent discontinuation: 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%]). In terms of cardiovascular events of interest: 1) a total of 0.1 % of mirabegron subjects discontinued secondary to atrial fibrillation or palpitations as did a similar percentage in the placebo group and 2) 4 (0.1%) mirabegron subjects discontinued due to tachycardia versus none in the placebo group. Abnormal liver function tests resulted in discontinuation in 3 (0.1%) mirabegron subjects versus 1 (0.1%) placebo subject. Skin rash was reported in 2 (0.1%) of mirabegron subjects leading to discontinuation versus 0 for placebo.

In the pivotal Phase 3 studies, the overall TEAEs reported by ≥3.0% of subjects were: hypertension 200/2736 (7.3) of mirabegron subjects versus 105/1380 (7.6%) placebo subjects, nasopharyngitis 94/2739 (3.4%) versus 35/1380 (2.5%), and urinary tract infections (UTI) 83/2736 (3.0%) versus 25/1380 (1.8%) for placebo. Subjects on mirabegron who reported hypertension were reviewed and the majority of subjects had hypertensive blood pressures noted prior to exposure to mirabegron.

Key safety issues for mirabegron include: cardiovascular safety (effects on blood pressure, heart rate, and cardiovascular AEs), neoplasms, hepatic safety, urinary tract related AEs, hypersensitivity reactions, and spontaneous pregnancies. These are outlined herein:

Cardiovascular Safety:

- **Blood pressure:**

A mirabegron-related elevation in blood pressure of approximately 1 mm Hg was observed in Phase 3 studies. Mirabegron-related elevations in blood pressure of approximately 3-4 mm Hg, however, were observed in the Phase 1 studies.

In the Phase 3 studies: Mirabegron 50 mg once daily was associated with an approximately 1 mm Hg increase from baseline in systolic and diastolic blood pressures (SBP/DBP) as compared with 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.

In the Phase 1 studies:

- *Study 178-CL-077, a thorough QT study, mirabegron at doses of 50 mg, 100 mg and 200mg, were associated with mean increases in SBP and DBP of 4.0, 7.7, 11.6 and 3.7, 4.1, 7.7mm Hg, respectively as compared to placebo at hours 3 or 6 post dose .*
- *Study 178-CL-031, in the first 8 hours post dose in healthy volunteers for mirabegron 50 mg, the maximum increases from baseline in SBP and DBP on Day 14 were 6.3 and 4.8 mmHg, respectively. In the same study, for placebo subjects, the maximum increases from baseline in SBP and DBP were 2.4 and 2.3 respectively for the same time period post dose.*

In these Phase 1 studies, there appeared to be a dose-responsive maximal increase in the blood pressure related to mirabegron.

The Phase 3 data are discussed in a separate document by the Division of Cardiovascular and Renal Products. The differences observed in Phase 1 and Phase 3 studies, and the clinical relevance of the mirabegron-related increases in blood pressure, will be further discussed during the meeting.

- **Heart rate:**

In the pivotal Phase 3 studies, mirabegron 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 (≥2, ≥5, ≥10 or ≥15bpm) in pulse rate in the 12 week pivotal studies were noted more frequently at various cut points with mirabegron than with placebo. In the Phase 1 study 178-CL-031, and in the TQT study, at doses of 50 mg and 200 mg, however, mirabegron was associated with maximal mean increases in pulse of 4.0 - 4.1and 10.3 to 11.8 bpm, respectively at one or more timepoints.

- **Cardiovascular adverse events:**

In the Global OAB safety database, the relative risk of major adverse cardiovascular events (MACE) was 0.24 (95%CI: 0.02, 1.69) for subjects receiving mirabegron compared with placebo. The 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 individual cases, it is unlikely that mirabegron is causative of atrial fibrillation. The paucity of reported events of hypertension and other major cardiovascular events may be related to the overall size of the safety databases, and does not resolve the concern related to blood pressure increases seen in the Phase 1 and 3 studies.

Neoplasms:

In the pivotal Phase 3 studies, there appears to be a difference between mirabegron and placebo in total number of neoplasm AEs when a variety of tumors, most instances reported by one subject, are added together. In addition, a higher incidence of SAEs reported as "neoplasms" was 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 1- year long, EU/NA Long-term Study. There is no known common mechanistic explanation to implicate mirabegron as related to any cancers or growth of existing tumors and based on review, some of these could have preexisted treatment. This

reported increased incidence of neoplasms, while of concern, occurred in the 100 mg mirabegron dose group and not in the to-be-marketed 50 mg dose group.

Urinary Tract Related AEs:

In the pivotal Phase 3 studies, the frequency of UTI was higher in mirabegron subjects compared with placebo subjects in the 12-week studies, and was similar to tolterodine subjects. 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 acute urinary retention (AUR) was reported in Japanese postmarketing data, there were no reports of AUR or clinically significant adverse increases in post void residual (PVR) volume in the submitted clinical trials.

Hepatotoxicity:

In the overall mirabegron development program there were reports of liver function test elevations and three reports of severe hepatotoxicity in association with hypersensitivity reactions in subjects taking mirabegron. One of these severe cases had a liver biopsy interpreted as drug-induced liver injury (DILI) or as autoimmune hepatitis. All three cases recovered or are in the process of recovering. In addition, two subjects in the Long-term Study had of ALT and AST to 10 times ULN with return to normal or baseline levels while continuing mirabegron 50 mg. Most of the cases of hepatotoxicity occurred in the setting of pre-existing liver function abnormalities, confounding medications, or as part of an allergic phenomenon, but there are cases where there were hepatic enzyme elevations in the absence of such phenomena. There was no clear dose response. Mirabegron may be associated with rare instances of hepatotoxicity.

Overall, it appears that mirabegron use may in some subjects cause hepatotoxicity.

Hypersensitivity reactions:

While there were no cases of anaphylaxis or angioedema reported, the incidence of plausible and related hypersensitivity events was higher in mirabegron subjects than it was in placebo subjects. In the non-immediate hypersensitivity category, there were 29 reports in mirabegron treated subjects, one in a placebo subject, and three in tolterodine subjects. There was one case of immediate hypersensitivity reaction in a 100 mg mirabegron subject (pruritis). Mirabegron was associated with the occurrence of significant hypersensitivity reactions, 7 of them were severe (2 cases of erythema multiforme [post marketing-Japan],(1) Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, (1) hemolytic anemia and (1)possible autoimmune hepatitis).

Glaucoma/Increased Intraocular Pressure:

In the Global Safety database, despite isolated reports of glaucoma and increases intraocular pressure during clinical trials, mirabegron did not appear to increase intraocular pressure based on results from a dedicated ocular safety study involving 310 healthy volunteers.

SUMMARY

Mirabegron is a beta-3-adrenoreceptor agonist and a new molecular entity for the treatment of overactive bladder in patients with symptoms of urge urinary incontinence, urgency, and urinary frequency. The efficacy of mirabegron was demonstrated in three randomized controlled trials using composite endpoints of 1) change from baseline in the mean number of incontinence episodes per 24 hours and 2) mean change from baseline in the mean number of micturitions per 24 hours. The key safety issues for mirabegron include cardiovascular safety (effects on blood pressure, heart rate, and cardiovascular AEs), neoplasms, hepatic safety, urinary tract related AEs, and hypersensitivity reactions.

The Division of Reproductive and Urologic Products seeks the advice of the Reproductive Health Drugs Advisory Committeee regarding the demonstration of efficacy and safety for mirabegron for the treatment of overactive bladder.

1. Review of Efficacy

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. The three pivotal Phase 3 studies that were analyzed by individual study and pooled for the efficacy analysis included: 178-CL-046, 178-CL-047 and 178-CL-074.

Not all subjects had incontinence at baseline; therefore, the Full Analysis Set (FAS) includes all subjects, and the Full Analysis Set-Incontinence (FAS-I) includes only those with incontinence at baseline.

1.1 Demographics

Populations in the mirabegron development program for were reflective of the OAB population that would receive the product after market approval. Inclusion and exclusion criteria in the Phase 3 studies were sufficiently broad to allow for subjects who were antimuscarinic treatment naive and subjects who received prior OAB antimuscarinic therapy. Subjects 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 subjects were ≥ 65 years of age and approximately 12% of subjects were ≥ 75 years of age across the treatment groups.

At baseline, the mean number of micturitions per 24 hours was 11.6 (in the FAS), and the mean number of incontinence episodes per 24 hours was 1.8 (in the FAS-I). All three types of OAB were represented, including urgency incontinence only, mixed stress/urgency incontinence with urge as predominant factor, and frequency/urgency without incontinence. Mean duration of OAB symptoms was similar across treatment groups, ranging from 85.2 to 88.3 months. The proportion of subjects with prior urological surgery for incontinence was relatively consistent across treatment groups, ranging from 8.3% to 9.5%. Approximately 52% of subjects received prior antimuscarinic OAB medications.

Demographics and OAB characteristics of the population enrolled were generally similar across the three primary Phase 3 studies.

Table 1: Summary Subject Demographics Phase 3 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)						
<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

FAS=Full analysis set; FAS-I= Full analysis set/incontinence at baseline

Source: Table 2, Summary of Clinical Efficacy (current submission), page 20.

1.2 Subject Disposition

Subject disposition in the three pivotal Phase 3 studies was further evaluated: 178-CL-046, 178-CL-047 and 178-CL-074.

For Study 178-CL-046, a total of 2437 subjects were screened, 2397 subjects entered the placebo run-in period, 2336 subjects received placebo run-in study drug, and 1987 subjects were randomized into the study. A total of 9 subjects 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 subjects 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 subjects were included in the FAS. Overall, 58.6% (1165/1987) of randomized subjects were included in the FAS-I, which was comprised of subjects in the FAS who had at least one incontinence episode in the baseline diary.

For Study 178-CL-047, a total of 2342 subjects were screened, 2306 subjects entered the placebo run-in period, 2149 subjects took placebo run-in study drug, and 1329 subjects were randomized into the study and 1328 received double-blind study medication (SAF population). The proportion of subjects 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 subjects 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 subjects were screened, 2060 subjects entered the placebo run-in period, 2030 subjects took placebo run-in study drug, 1306 subjects were randomized into the study, and 1305 subjects received study drug. The proportion of subjects 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 subjects were included in the FAS and 59.2% (773/1306) were included in the FAS-I.

1.3 Analysis of Primary Endpoints

The pivotal analysis set included efficacy data from the three Phase 3 Studies (178-CL-046, 178-CL-047 and 178-CL-074). In the studies, three doses were evaluated in some of these studies: 25 mg, 50 mg, and 100 mg. Of these three doses, the Applicant has requested consideration of only two doses: 50 mg and 25 mg. Only those two doses will be described. The three studies are outlined below in Table 2.

Table 2: Overview of pivotal analysis studies

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-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-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

All three pivotal Phase 3 studies included co-primary endpoints of the change from baseline to endpoint in:

1) Mean number of incontinence episodes per 24 hours as compared to placebo, and
2) Mean change from baseline to endpoint in the mean number of micturitions per 24 hours as compared to placebo.

Pooled results for these co-primary endpoints are outlined in Tables 3 and 4 below. Individual study results are presented in Tables 5, 6, and 7. The efficacy results are shown both as pooled data and by individual study to give all overall picture of efficacy. We have pooled the data for illustrative purposes because the studies were similarly designed.

Table 3: Change From Baseline to Final Visit in Mean Number of Incontinence Episodes per 24 hours, Pooled Primary Studies (in FAS-I population)

	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 significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only.				

Sources: Table 38, Integrated Summary of Efficacy, page 143: Table 17, 178-CL-074 Study Report, page 105.

† Mirabegron 100 mg is not under consideration for marketing for this application

Table 4: Change from Baseline to Final Visit in Mean Number of Micturitions per 24 hours, Pooled Primary Studies (in FAS population)

	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 significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only.				

Sources: Table 39, Integrated Summary of Efficacy, page 147: Table 18, 178-CL-074 Study Report, page 106.

† Mirabegron 100 mg is not under consideration for marketing for this application

Table 5: Primary and Key Secondary Efficacy Endpoint Results Study 178-CL-046

	Mirabegron		
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	
Adjusted mean difference vs placebo(SE)	**-0.41 (0.160) p=0.003**	-0.29 (0.162) p=0.010	
Change from baseline to Final Visit in Mean Number of Micturitions per 24 hr (FAS)			
N	**473**	478	
Adjusted mean difference vs placebo(SE)	**-0.60(0.156) p=<0.001**	-0.44(0.156) p=0.005	
Key Secondary Efficacy Results			
Change From Baseline to Final Visit in Mean Volume per Micturition (mL) (FAS)			
N	**472**	478	
Adjusted mean difference vs placebo(SE)	**11.9 (2.83) p=<0.001**	13.2 (2.82) p=<0.001	
Change from Baseline to Week 4 in Mean Number of Incontinence Episodes per 24 hr (FAS-I)			
N	**293**	281	
Adjusted mean difference vs placebo(SE)	**-0.39 (0.167) p=0.002**	-0.38 (0.169) p=0.002	
Change From Baseline to Week 4 in Mean Number of Micturitions per 24 hr (FAS)			
N	**471**	477	
Adjusted mean difference vs placebo(SE)	**-0.40 (0.136) p=0.004**	-0.52 (0.136) p=<0.001	

Source: Table 1, Summary of Clinical Efficacy

† Mirabegron 100 mg is not under consideration for marketing for this application

Table 6: Primary and Key Secondary Efficacy Endpoint Results Study 178-CL-047

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, Summary of Clinical Efficacy, page 9

† Mirabegron 100 mg is not under consideration for marketing for this application

Table 7: 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.

The pooled primary efficacy analysis demonstrated:

For the co-primary endpoints of reduction in incontinence episodes (FAS-I) and reduction in micturitions over 24 hours (FAS):

- **Treatment with mirabegron 50 mg resulted in a reduction of incontinence episodes per 24 hours as compared to placebo of -0.40 (p<0.001 corrected for multiplicity).**

- **Treatment with mirabegron 50 mg resulted in a reduction of micturitions per 24 hours as compared to placebo of -0.75 (p<0.001 corrected for multiplicity).**

The mirabegron 100 mg dose is not being considered for marketing approval.

The mirabegron 25 mg dose is being considered for approval only in specific populations (severe renal impairment and moderate hepatic impairment) due to pharmacokinetic (PK) considerations.

1.4 Analysis of Secondary Endpoints(s)

The key secondary endpoints were volume voided per micturition, number of incontinence episodes per 24 hours at Week 4, and number of micturitions per 24 hours at Week 4 in a statistically gated order of testing.

The mirabegron 50 mg dose is being considered for marketed in this application. However, studies included doses of 25 mg and 100 mg.

In pooled and individual study analyses, mirabegron at both the 50 and 100 mg doses increased mean volume voided per micturition (Table 8). 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. Therefore, the adjusted mean placebo-subtracted differences were 11.9 mL (mirabegron 50 mg) and 12.3 mL (mirabegron 100 mg).

The mirabegron 25 mg group, evaluated only in Study 074, did not achieve a statistically significant change in mean volume voided. The efficacy of the 25 mg mirabegron dose was tested only in Study 178-CL-074. Based on the gatekeeping procedure further secondary endpoints for the mirabegron 25 dose were not tested.

Table 8: 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 significantly superior compared with placebo at the 0.05 level with multiplicity adjustment.				
The mirabegron 25 mg results are from Study 178-CL-074 only.				

Sources: Table 20, 178-CL-074, page 111: Table 40, ISE, page 151.

† Mirabegron 100 mg is not under consideration for marketing for this application

Mirabegron 50 mg demonstrated a 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 effectiveness was maintained throughout the treatment period (through weeks 8 and 12).

In pooled and individual study analyses, the 50 mg and 100 mg mirabegron groups demonstrated a statistically significant reduction from baseline to Week 4 in mean number of incontinence episodes per 24 hours compared with placebo with multiplicity adjustment (Table 9). The 25 mg mirabegron dose did not (not shown).

Table 9 and 10 show the change from baseline to week 4 in mean number of daily incontinence episodes and micturitions, respectively.

Table 9: 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 significantly superior compared with placebo at the 0.05 level with multiplicity adjustment			

Source: Table 41, ISE, page 153

† Mirabegron 100 mg is not under consideration for marketing for this application

Table 10: 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 significantly superior compared with placebo at the 0.05 level with multiplicity adjustment			

Source: Table 42, ISE, page 154.

† Mirabegron 100 mg is not under consideration for marketing for this application

1.5 Other Endpoints

The mirabegron studies included a variety of tertiary (exploratory) endpoints, including measurement of urinary "urgency". The content validity of these endpoints, including measures of "urgency", remains under discussion at FDA as to whether the assessment

instruments are "fit" for purpose of labeling. The results of these endpoints are currently considered exploratory for this NDA. Nonetheless, the results are shown here because these endpoints assess subjective aspects of OAB and serve to inform the interpretation of the primary and secondary endpoints.

The adjusted mean changes from baseline to final visit for urgency incontinence episodes per 24 hours 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 urgency incontinence episodes compared with placebo.

The mean number of severe urgency (Grade 3 or 4) episodes per 24 hours at baseline was comparable across all treatment groups in the pooled primary studies. Severe urgency grade was defined by the Patient Perception of the Intensity of Urgency Scale (the PPIUS) as "I could not postpone voiding, but had to rush to the toilet in order not to wet myself." Grade 4 urgency was defined 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 for severe urgency episodes, defined as shown, 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 subject went to bed with the intention to sleep until the time the subject got 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 in nocturia episodes 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 (Full Analysis Set- Incontinence) 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 subject 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 complete responders (zero incontinence at final visit) 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 complete responders, defined as zero incontinence episodes.

The criterion for a responder with ≥50% reduction in incontinence episodes required that a subject have a ≥ 50% decrease from baseline to final visit in mean number of incontinence episodes per 24 hours. At the final visit, the percentage of "50%" responders was 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 ≥50% reduction from baseline to final visit in mean number of incontinence episodes per 24 hours.

The criterion for a "micturition" responder, defined as ≤ 8 micturitions per 24 hours, required that a subject 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 Treatment Satisfaction Visual Analogue Scale (TS-VAS), subjects 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 subjects with OAB, compared with placebo.

1.6 Subpopulations

A clinical perspective is provided on the following subgroup analyses. The subgroup analyses shown below are based upon pooled data and should be considered as exploratory from a formal statistical perspective. Nonetheless, the data provides perspective on the overall efficacy results.

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 subjects (adjusted mean difference from placebo: -0.47 and -0.47, mirabegron 50 and 100 mg groups, respectively) compared with male subjects (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 subjects. Due to the smaller sample sizes for male subjects in the FAS-I, the confidence intervals were larger compared with those observed in female subjects. It should be noted that baseline mean values for incontinence episodes were lower in male subjects (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 subjects (2.86, 2.83 and 2.94 episodes per 24 hours in the placebo, mirabegron 50 mg and mirabegron 100 mg groups, respectively).

Thus, male subjects were less likely than female subjects to have incontinence at baseline and they demonstrated a higher placebo mean adjusted change from baseline. The small numbers of males in the studies relative to females serves to limit the studies' ability to demonstrate an appreciable reduction in incontinence in males.

The baseline mean number of micturitions per 24 hours for male and female subjects 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 subjects was -0.92, -1.29 and -1.62, respectively and the reduction in female subjects was -1.31, -1.93 and -1.79, respectively. Among male subjects, 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 subjects, 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.

The effect of mirabegron treatment in male subjects with OAB overall with regard to the co-primary endpoints is smaller than in women with OAB, but still consistent with an overall positive effect.

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).

In the subpopulation analysis of subjects 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 subjects < 65 and ≥ 65 years and for subjects < 75 and ≥ 75 years of age. Thus, for daily episodes of incontinence, it appears that the older population subgroups have increased efficacy compared with younger subgroups. With respect to frequency of micturitions, the > 65 years of age subpopulation also has improved efficacy as compared to the < 65 years of age subgroup.

Race

In the subpopulation analysis of subjects 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 subjects in the categories "Asian" and "Other" to draw meaningful conclusions about these groups. Overall, there is an effect in all racial subgroups, but the small number of subjects in non-White groups precludes meaningful conclusions from these analyses.

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.

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.

Intrinsic/Extrinsic Factors

A summary of important baseline characteristics is provided in the table below.

Table 11: Summary of Intrinsic/Extrinsic Factors at Baseline: Pooled Analysis of 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

Benign Prostatic Hyperplasia (BPH)

Mirabegron 50 and 100 mg did not appear effective in decreasing the mean number of incontinence episodes in men with BPH. The to-be-marketed 50 mg mirabegron dose had only a modest effect on decreasing micturition episodes in men with BPH – See table below.

Table 12: 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)
	Yes	Adjusted Difference vs Placebo							
			Mean		0.14	0.03		-0.16	-0.87
	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)
	No	Adjusted Difference vs Placebo							
			Mean		-0.09	0.04		-0.48	-0.50

Source: Table 55, ISE, page 203

Diabetes

In diabetic subjects, mirabegron 50 mg and 100 mg decreased daily incontinence episodes (adjusted difference versus placebo) by -0.38 and -0.41 respectively. In diabetic subjects, mirabegron 50 mg and 100 mg decreased daily micturitions (adjusted difference versus placebo) by -0.78 and -0.83 respectively. This does not appear to be clinically different between groups.

Renal Status

In subjects 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.

Beta-Blocker Use

After review, it appears that subjects using beta-blockers have similar efficacy results compared to subjects not on ongoing beta-blockers.

Diuretic Use

In subjects with concomitant diuretic use, the efficacy of both mirabegron 50 mg and 100 mg was superior to the efficacy to that of subjects not on diuretic use and exceeded the efficacy results in the overall study population for the primary efficacy endpoints.

Alpha-1-Antagonist Use (Males only)

Mirabegron 50 mg reduced the daily incidence of incontinence episodes in males taking alpha blockers similarly to the reduction in the overall study population. The reduction in the number of daily micturitions in this subpopulation was smaller than that in the overall study population (-0.12 versus -0.55). For the100 mg dose of mirabegron, the converse was true.

The numbers of subjects using alpha blockers was too small to draw meaningful conclusions.

1.7 Analysis of Efficacy Results for Dosing Recommendations

The Applicant's considerations for selecting the 50 mg starting dose included:

- The 25 mg dose was tested in just one Phase 3 study (Study 178-CL-074 only).
- Overall, mirabegron 50 mg achieved more statistically significant effects on efficacy endpoints than mirabegron 25 mg.
- Therapeutic effect at 4 weeks was not demonstrated for mirabegron 25 mg.
- Measures of urgency, which include the mean level of urgency, the mean number of Grade 3 or 4 urgency episodes, and the change in baseline in mean level of urgency all showed a numerical reduction for mirabegron 50 mg. The mean level of urgency was also statistically significantly reduced at endpoint as compared to placebo. On the other hand, 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 demonstrated numerically improved results for these measures, the improvement with mirabegron 50 mg was numerically greater than with the 25 mg dose.
- An "urgency responder" was defined as a subject with a decrease from baseline to final visit in mean level of urgency which was at least as large as the what the Applicant considered to be the minimally important difference (MID) for this measure. The Applicant proposed that 0.24 was the MID for this measure. At the final visit, the percentage of responders defined in this manner 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. Statistical significance was achieved for the mirabegron 50 mg group.

- In incontinent subjects who required pad use, there was a reduction in the mean number of pads used per 24 hours from baseline to final visit only in the 50 mg group; 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 suggested improved patient reported outcomes for mirabegron 50 mg daily as compared to mirabegron 25 mg daily.
- For the WPAI:SHP (Work Productivity and Activity Impairment) questionnaire, 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 for overall work impairment.

The Applicant's rationale for dose selection is reasonable and appropriate.

1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study 178-CL-049 was an active-controlled, 1-year study that was principally intended to provide safety information, but also provided some evidence regarding 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. Since subjects "rolled over" into Study 178-CL-049 from previous clinical studies of mirabegron, the analyses of the efficacy endpoints were adjusted for prior treatment and study experience. Overall, 74.2% and 85.3% of subjects were female (FAS and FAS-I, respectively). 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.

1.9 Additional Efficacy Issues/Analyses

In the primary Phase 3 studies, subjects were instructed to take medication in the morning with a glass of water, with or without food. Mirabegron 50 mg was effective when administered with or without food. For additional FDA comments related to mirabegron and food, the reader is referred to the FDA's Clinical Pharmacology briefing document.

Tolterodine was included as a treatment arm in some of the Phase 3 studies. In some cases, subjects were allowed to enroll if they had previously used tolterodine and no longer wanted to continue use. Therefore, direct efficacy comparisons to tolerodine use were not possible with the submitted data.

Both mirabegron 50 and 100 mg doses were effective in reducing the mean number of incontinence episodes and micturitions per 24 hours in antimuscarinic treatment naïve subjects as well as in subjects that had received previous OAB antimuscarinic therapy. In subjects with previous OAB antimuscarinic therapy both mirabegron 50 and 100 mg doses were effective in reducing the placebo-corrected mean number of micturitions per 24 hours and mean number of incontinence episodes in subjects discontinuing secondary to poor tolerability. The results in this subpopulation were comparable in both instances to the results in the general patient population.

2 Review of Safety

2.1 Methods

2.1.1 Clinical Studies Used to Evaluate Safety

The safety analysis focused on the safety results in the pivotal Phase 3 study population (Studies 178-CL-046, 178-CL-047, and 178-CL-074) and the controlled study population of longest duration, the EU/NA Long-term Controlled Population (Study 178-CL-049, also referred to as the "long-term controlled study"). Other Phase 3 and or Phase 2 studies are included in this safety summary in as part of integrated study population (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), or individually, if deemed appropriate. The reader is referred to Table 2 of this review for summaries of each study.

Safety evaluations included four doses: mirabegron 25 mg, 50 mg, 100 mg and 200 mg. Tolterodine was also used in some studies as an active comparator and assisted in the evaluation of some of the safety issues. There are no currently approved beta-3-adrenoreceptor agonists approved for the US market that can be used for comparison of safety data. Mirabegron was recently approved in Japan, and some postmarketing data are available.

Table 13: Summary of Clinical Studies with Mirabegron Included in Submission

Study Identifier: Sites	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 **14 European Countries**	Dose-response for efficacy; safety and tolerability of mirabegron	Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging	mirabegron 25, 50, 100, 200 mg tolterodine SR 4 mg 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 **Japan**	Dose-response for 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 **Europe and Australia**	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active controlled	mirabegron 50 or 100 mg, tolterodine SR 4 mg 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 **Canada, United States**	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	mirabegron 50 or 100 mg 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 **Japan**	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo- and active-controlled	mirabegron 50 mg, tolterodine SR 4 mg 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	mirabegron 50 or 100 mg tolterodine ER 4 mg	2452 adults with OAB	12 month double-blind treatment period
178-CL-074 **Canada, Europe and United States**	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	mirabegron 25 or 50 mg 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 **Europe**	Efficacy, safety, tolerability, population PK; proof of concept	Phase 2a, randomized, double-blind, parallel group, placebo-controlled and active controlled	placebo, mirabegron IR 100 or 150 mg bid, 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 **Canada and United States**	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	Mirabegron IR 60, 130, 200 mg tablet matching placebo po; once daily after breakfast	200 men with LUTS and BOO	12-week DB treatment period

178-CL-003 **Poland**	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	Mirabegron IR 60, 130, 200 mg tablet 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
178-CL-004 **Poland**	PD, safety, tolerability, PK	Phase 2a, placebo controlled, dose titration study	Mirabegron IR 60, 130, 200 mg tablet matching placebo po; once daily after breakfast Metformin 500 and 850 mg tablets po;	60 adults with Type 2 diabetes on stable metformin monotherapy	4-week single-blind placebo run-in followed by 12-week double blind treatment period

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

The total number of subjects in the Global Phase 2/3 Population is 5,865. This population includes all subjects 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]), indications (OAB, Lower Urinary Tract Symptoms in Men with Bladder Outlet Obstruction [LUTS/BOO], type 2 diabetes mellitus), mirabegron formulations (but mostly the extended release [OCAS] formulation), study designs (double-blind, open-label) and geographic locations (Europe, North America, Japan, Australia/New Zealand, South Africa). Where possible the primary focus of the safety analysis will be the pivotal Phase 3 population. Occasionally, the Global Phase 2/3 12 week OAB population (limited to those studies of 12 weeks in duration), will be referred to as it is a larger numerical group when it informs the discussion.

AE terms of special interest, including those related to the cardiovascular (CV) system, hypersensitivity, glaucoma and neoplasms, are presented separately below.

Table 14: Numbers of Subjects Treated in the Phase 2/3 Clinical Studies

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
	453		442	433		875		
178-CL-047	433	432	440			872		
178-CL-074								
Phase 3 Total Population	1380	432	1375	929		2736		495
178-CL-044	169	169	169	168	167	673		85
	213	210	208	208		626		
178-CL-045	380		379			379		
178-CL-048								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 15: Numbers of Subjects Treated in the Long Term Clinical Studies

Study	**Mirabegron mg/day 50mg**	**100mg**	**New Exposure**	**Re-Exposure**	**Tolterodine ER 4 mg**
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

2.1 Overall Exposure

Table 16 summarizes patient exposure to mirabegron in the global safety database.

Table 16: 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

The overall patient exposure to mirabegron and duration of exposure is adequate to estimate safety of mirabegron at the to-be-marketed doses and duration of use.

In the Global Phase 2/3 Population, 4399/5863 (75.0%) mirabegron subjects were female. Overall, 4387/5858 (74.9%) subjects 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 subjects 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%) subjects were ≥ 65 years of age and 574/5863 (9.8%) subjects were ≥75 years of age. The mean body mass index (BMI) was 27.5 kg/m2. The largest proportion of subjects were in the < 25 kg/m^2 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 subjects. Overall, 4310/4611 (93.5%) subjects 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%) subjects were Black or African American, 49/4611 (1.1%) were Asian and 29/4611 (0.6%) were "Other"; 2484/2633 (94.3%) of subjects were not Hispanic or Latino. The median age was 61.0 years of age; 1744/4611 (37.8%) subjects were ≥ 65 years of age and 499/4611 (10.8%) subjects were ≥75 years of age. The mean BMI was 29.0 kg/m^2. The largest proportion of subjects were in the 25 to < 30 kg/m^2 BMI group (1715/4608 [37.2%]) and were from Europe (2565/4611 [55.6%]); all tolterodine subjects (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%) subjects were female, 2332/2444 (95.4%) subjects were White and 2367/2442 (96.9%) subjects were non-Hispanic and non-Latino. The median age was 61.0 years of age. Overall, 908/2444 (37.2%) subjects were ≥ 65 years of age and 239/2444 (9.8%) subjects were ≥75 years of age. The mean BMI across all treatment groups was 28.8 kg/m^2. The largest proportion of subjects were in the 25 to < 30 kg/m^2 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 Study 044, and the Japanese Phase 2 and Phase 3 Studies 044 and 048, respectively) for the 25, 50, and 100 dose groups of mirabegron.

Thus, the Phase 3 study population was similar to those of other approved OAB products and consisted primarily of older, white women.

2.2.2 Explorations for Safety Dose Response

The EU/NA OAB 12-week Phase 3 Population includes 2736 subjects treated with mirabegron, 1380 subjects treated with placebo and 495 subjects 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%) of mirabegron subjects, respectively, and by 29/1380 (2.1%), 658/1380 (47.7%) and 46/1380 (3.3%) of placebo subjects, respectively, and finally, by 11/495 (2.2%), 231/495 (46.7%) and 22/495 (4.4%) of tolterodine subjects, respectively. There was no apparent dose response across mirabegron groups (see Table below). These trends were similar to those observed with the Global OAB 12-week Phase 2/3 Population.

Table 17: 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 subjects received mirabegron 200 mg a day (Study 178-CL-044). There were no deaths in the 200 mg group. There were 3 SAE's (1.8%) in the 200 mg group. 7 subjects (4.2%) discontinued secondary to an AE in the 200 mg group. 80 (47.9%) subjects experienced an adverse event while using mirabegron 200 mg (Table 5.1.2 ADAE datatset, ISS/SCS).

The Applicant has conducted an adequate dose exploration for assessment of safety. Small elevations of the QTc interval were noted only in female subjects and only at the supratherapeutic dose of 200 mg dose of mirabegron at 5 hours post dose (10.42 milliseconds) as compared to placebo in Study 178-CL-077. The to be marketed dose is 50 mg for most patients, and 25 mg for specific populations.

2.3 Major Safety Results

2.3.1 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 subjects participating in completed trials (5 subjects treated with mirabegron, one treated with placebo and 3 treated with tolterodine). It is not possible to attribute these deaths directly to mirabegron. The deaths in the 3 pivotal studies and in the 52 week long-term safety study are listed below.

- 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 subject 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 subject'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 subject died within minutes of onset. Although the subject's blood pressure was somewhat high, both before and after initiation of study drug treatment, it fluctuated only slightly during treatment 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 subject 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 subject also received mirabegron 100 mg in Study 178-CL- 047.

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.

2.3.2 Nonfatal Serious Adverse Events

In the Global OAB 12-week Phase 2/3 Population, one or more SAEs was reported for 77/4414 (1.7%) mirabegron, 38/2142 (1.8%) placebo and 16/958 (1.7%) tolterodine subjects, 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).

The table below highlights the SAEs reported in the 12 week EU/NA Phase 3 pivotal studies:

Table 18: Serious Treatment Emergent Events in Safety Analysis Set (MedDRAv12.1): 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
		25 mg N=432	50 mg N=1375	100 mg N=929	Total N=2736	ER 4 mg N=495
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**	**3(0.2)**	**4 (0.4)**	**7 (0.3)**	**1 (0.2)**

and Procedural Complications	**(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
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

From a clinical perspective, in regard to the SAEs reported in the Phase 3 studies:

- 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.

- There was no apparent difference in SAEs in females as compared to males except in the EU/NA Phase 3 Study population where SAEs were reported in 23/786 (2.9%) males and 39/1950 (2.0%) females who were taking mirabegron.

- A small difference in the incidence of atrial fibrillation as an SAE in the mirabegron group over the placebo group was reported.

- There appears to be a small difference in the number (incidence) of serious infections noted in subjects dosed with 50 mg of mirabegron (n=7) versus placebo (n=4). These infections are single occurrences for 7 different preferred terms for mirabegron 50 mg and are single occurrences for 4 different preferred terms for placebo subjects. There were no serious urinary tract infections noted in subjects receiving mirabegron 50 mg.

- A difference was reported between mirabegron and placebo in the total number of neoplasms reported as an SAE when a variety of differing tumors, each reported by 1 subject, are added together. This difference is driven by results in one study (178-CL-047). When these cases were analyzed, most were found to be pre-existing.

- A total of three reports of urolithiasis as an SAE in the mirabegron group versus none in the placebo group.

- A single report of "hypertensive crisis" should have been classified as hypertension.

- There are several isolated reports of SAE traumatic injuries in mirabegron treated subjects versus none with placebo. Additional information was obtained from the Applicant regarding each case. 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:

- No increased incidence of atrial fibrillation in the mirabegron group compared to the tolterodine group (0.4% versus 0.1% respectively) was noted.
- Four reports of liver function abnormalities (0.1 %) versus none for tolterodine.
- In the Neoplasms, Benign and Malignant (including cysts and polyps) SOC, in the mirabegron 50 mg dose group, 1 (0.1%) reported a neoplasm SAE, while 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.
- One report of hypertension in each of the mirabegron treatment groups (0.1%) versus none in the tolterodine group.

Table 19: SAEs (>= 2 patients in the Total Mirabegron Group), EU/NA Long-Term Controlled Population (Study 178-CL-049)

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)	Mira 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%)
Abscess Intestinal	**1 (0.1%)**	1 (0.1%)	2 (0.1%)	0
Investigations	**1 (0.1%)**	3 (0.4%)	4 (0.2%)	0
Liver Function Test Abnormal	**0**	2 (0.2%)	2 (0.1%)	0
Musculoskeletal 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

From a clinical perspective of the SAEs reported in the long-term controlled study:

- Atrial fibrillation: Three 50 mg mirabegron subjects were noted to have atrial fibrillation in Study 178-CL-049.

- Hypertension: 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.

- Liver function test abnormalities: Three subjects in the mirabegron 100 dose arm had reports of abnormalities of liver function tests.

- With respect to CVA, subject 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 Neoplasms, the reader is referred to the Adverse Events of Special Interest section.

2.3.3 Dropouts and/or Discontinuations

The EU/NA OAB 12-week Phase 3 Population studies included 4611 subjects (2736 mirabegron, 1380 placebo and 495 tolterodine subjects) 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 subjects completed the double-blind treatment period, while 307/2736 (11.2%) mirabegron, 175/1380 (12.7%) placebo and 50/495 (10.1%) tolterodine subjects 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%]).

In addition, 0.1 % of mirabegron subjects discontinued secondary to atrial fibrillation or palpitations as did a similar percentage in the placebo group. Four (0.1%) mirabegron subjects discontinued due to tachycardia versus none in the placebo group. Abnormal liver function tests resulted in discontinuation in 3 (0.1%) mirabegron subjects versus 1 (0.1%) placebo subject. Skin rash was reported in 2 (0.1%) of mirabegron subjects leading to discontinuation versus 0 for placebo. "Hypertensive crisis" was reported in 2 (0.1%) of mirabegron 50 mg subjects.

In the Phase 3 EU/NA Study Population, the following are worthy of mention:

- Discontinuations due to liver function abnormalities are greater in the mirabegron group than the placebo group. Three subjects had mild elevations of LFTs (3312-3435[046], 2252-8275[047] and 2053-7047[079]). In all three cases, improvement of liver enzyme levels was reported after discontinuation of mirabegron. This suggests an association of liver function abnormalities and mirabegron.

- 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 cases were analyzed (Patient 3028-2466[046] and Patient 3086-1834[046]). They did not meet the criteria for hypertensive crisis and are more appropriately classified 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. This may suggest an association of worsening hypertension and mirabegron.

- Discontinuation due to atrial fibrillation – four mirabegron subjects 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. In the three other reports of atrial fibrillation, there appeared to be meaningful confounding factors that made interpretation difficult.

- Discontinuations related to tachycardia and palpitations: Four subjects reported tachycardia in mirabegron subjects. Patient 3132-71820(074) was randomized to mirabegron 25 mg and on Day 1 dizziness and tachycardia were reported. The subject 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. There were also 3 events of palpitations leading to discontinuation. Tachycardia and palpitations appear to be associated with mirabegron use.

- Discontinuations due to Skin and Subcutaneous adverse events were greater in the mirabegron group compared to placebo. Although no skin-related adverse

event Preferred Term was reported in greater than 1 subject, there were multiple, single terms (n=5) possibly indicative of an allergic or hypersensitivity phenomenon with mirabegron.

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 subjects (mirabegron 50 mg: 48/812 [5.9%]; mirabegron 100 mg: 50/820 [6.1%]) and 46/812 (5.7%) tolterodine subjects. 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%]).

In addition, palpitations were noted in 2 (0.2%) of mirabegron 100 mg subjects. 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 subjects and 0 mirabegron 50 mg subjects.

A total of six (0.4%) mirabegron subjects and four (0.5) 50 mg subjects discontinued secondary to hypertension compared to 3 (0.4%) tolterodine subjects. The increased incidence of neoplasms has been discussed under SAEs.

Table 20: EU/NA Long Term Controlled Population TEAE Leading to Discontinuation by SOC where Total Mirabegron Group Exceeds Tolterodine ER 4

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 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 (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

In regard to the discontinuations in the Long-Term Study 049, the following is worthy of note:

- Hypertensive crises and adverse events were previously discussed and may reflect 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 subjects had pre-existing labile hypertension and the remaining five had exacerbations of pre-existing hypertension. Exacerbation of pre-existing hypertension may be a direct result of mirabegron given the known effects on blood pressure and heart rate.

- Skin and subcutaneous AEs are discussed in a subsequent section of this report.

- Malignancy AEs will be discussed in the next section of this report.

2.3.4 Commonly Reported Adverse Events

In the EU/NA OAB 12-week Phase 3 Population, the most common TEAEs (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 subjects. For placebo, the maximum TEAE severity was mild for 26.4%, moderate for 17.5% and severe for 3.8% of subjects; for tolterodine the maximum TEAE severity was mild for 26.1%, moderate for 17.2% and severe for 3.4% of subjects.

The were no AEs by preferred terms or total by SOC where the incidence in the mirabegron 50 arm exceeded that in the placebo arm by one percent or greater (Table 5.2.3.1 ADAE Dataset, ISS).

The table below illustrates the incidence of AEs ≥ 3.0% in the total EU/NA Phase 3 12 Week Population:

Table 21: TEAE by PT (reported by >=3.0% in Total Mirabegron Group) EU/NA Phase 3 Population

MedDRAv12.1 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 22: TEAE by PT (reported by >=3.0% in the Total Mirabegron Group) EU/NA Long-Term Controlled Population

MedDRAv12.1 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.

2.3.4.1 Commonly Reported AEs by Subgroup

2.3.4.1.1 Commonly Reported AEs by Gender

The frequency of commonly reported TEAEs was modestly higher in female subjects compared with male subjects across treatment groups in the 12-week 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 in the Phase 3 studies by gender were:

Table 23: TEAEs by Gender - 12 Week 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

2.3.4.1.2 Commonly Reported AEs by Age

The frequency of TEAEs reported was modestly higher in subjects ≥ 65 years of age compared with subjects < 65 years of age across treatment groups in the OAB 12-week Phase 3 Population. For mirabegron, the difference from placebo or from tolterodine was generally similar between age groups.

Table 24: TEAE 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

2.3.4.1.3 Commonly Reported AEs by Alpha-Adrenergic Blocker on Beta-Blocker Use

Men with symptomatic BPH may report overactive bladder symptoms. Therefore, it is possible that mirabegron could be used concomitantly with alpha-adrenergic antagonists, a class of drugs commonly used to treat BPH, and also still used to treat hypertension.

The use of alpha 1–adrenergic blockers at baseline was associated with a lower frequency of TEAEs in the total mirabegron and placebo groups in both the 12 week and long term studies compared to non-users of alpha-1 blockers. On the other hand, the frequency of SAEs and TEAEs leading to discontinuation was higher in both the 12 week and in the long term study subjects using alpha 1–adrenergic blockers at baseline than in subjects

who were not (long term study: 10.6% in alpha blocker users versus 4.8% in non-alpha blocker users for 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 incidence of hypertension was increased in subjects using alpha 1–adrenergic blockers at baseline in the 12 weeks studies (Table 202, ISS, page 394). The increased incidence of hypertension was also noted in the 100 mg subjects in the long-term study in subjects using alpha 1–adrenergic blockers at baseline.

These increased incidences of SAEs and TEAEs leading to discontinuation in baseline alpha 1-adrenergic blocker users may be a reflection of the adverse reactions associated with the alpha adrenergic blocker class. It is difficult to separate this finding from a drug-drug interaction.

There were no notable safety issues in subjects using beta blockers at baseline.

2.3.5 Adverse Events of Special Interest

The adverse events of special interest in this submission were:

- Increased intraocular pressure and reports of glaucoma
- Neoplasms reported in short and long-term studies
- Urinary tract AEs, including UTI, acute urinary retention, and urolithiasis
- Hepatotoxicity as evidenced by increases in liver function tests
- Endocrine and metabolic potential adverse effects, for example, potential effects on glucose metabolism
- Cardiovascular safety, including increases in blood pressure and hypertension AEs, atrial fibrillation AEs, increases in pulse and AEs of tachycardia and palpitations, and the potential for QT prolongation.
- Hypersensitivity reactions

In this section of the review, each of these areas of special interest are discussed individually.

2.3.5.1 Increased Intraocular Pressure and Glaucoma:

Following the report of 2 serious adverse events (SAE) of glaucoma, the Applicant conducted a systematic evaluation of adverse events representing glaucoma during the mirabegron clinical program. Subsequently, the FDA Review Division requested a dedicated study to assess the effect of mirabegron on intraocular pressure (IOP).

- Study 178-CL-081 was a randomized, double-blind, placebo-controlled, non-inferiority study to assess the effect of mirabegron on IOP. A supratherapeutic

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 only in placebo-treated subjects and no discontinuations for IOP were reported. Visual acuity and biomicroscopy data were generally unremarkable in this study with no reported glaucoma type AE.

- Astellas conducted a systematic evaluation of glaucoma-type AEs in all completed clinical studies within the global mirabegron clinical development program which included 8752 subjects (5863 mirabegron-treated subjects) and 1000 mirabegron-treated healthy volunteers. The percent of subjects with glaucoma events based on the expert panel assessment in the Global OAB 12-week Phase 2/3 Population was 0% [0/2142 subjects; 95% CI: 0.00%, 0.17%] for placebo, < 0.1% [2/4414 subjects; 95% CI: 0.01%, 0.16%] for mirabegron, and 0% [0/958 subjects; 95% CI: 0.00%, 0.38%] for tolterodine [Table 5.1]. In the EU/NA Long-term Controlled Population the percent of subjects with glaucoma events based on the expert panel assessment was 0.1% [2/1632 subjects; 95% CI: 0.01%, 0.44%] for mirabegron and 0.1% [1/812 subjects; 95% CI: 0.00%, 0.68%] for tolterodine.

This evidence does not support an association between mirabegron and increased intraocular pressure.

2.3.5.2 Neoplasms

In the EU/NA Long-term Controlled Study 178-CL-049, the number of SAEs 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. These and other related results are shown in detail in this section.

In the short-term studies; that, is in the Global OAB 12-week, Phase 2/3 Population consisting of 6 studies, the number of serious adverse events in the category of neoplasms benign, malignant and unspecified (including cysts and polyps), were higher in the total mirabegron group compared with placebo group (10 new malignant events were reported in 9 mirabegron subjects). 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 reported neoplasm SAEs were heterogeneous and represented benign as

well as malignant events, generally reflecting the most prevalent malignancies in the US and Europe.

In the long-term study, 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 adverse events of neoplasia 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. Subjects in previous Phase 3 studies (178-CL-046 and 178 CL-047) and treatment naïve subjects were allowed to enroll in Study 178-CL-049.

In the EU/NA Long-term Controlled Population, the overall frequency of subjects with new malignant events was 12/1632 (0.74%) in the total mirabegron group compared with 4/812 (0.49%) in the total tolterodine group. The RR of new malignant events for the total mirabegron group compared with the total tolterodine group was 1.50 (95% CI: 0.45, 6.38). A total of 21 events were reported in 16 subjects across 7 tumors organs of origin.

The table and narratives that follow below represent an analysis of neoplasms from Study 178-CL-049.

Table 25: 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?	Additional Information: Adjudication Comments
Mirabegron 50 mg				
2179-6744 54/White/Female US	Endometrial Cancer Stage I	315/350 (364)	Placebo (047)	Heavy Vaginal Bleeding x 1yr: "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	Pancreatic Carcinoma	323/376 (323)	Tolterodine SR	Initial symptoms

Germany			4 mg (046)	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 to 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 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.

Neoplasm AE Narratives

Subject 2179-6744: Grade I Endometrial Cancer: The subject is a 54 year old white US female randomized to mirabegron 50 mg on 4 December 2008. 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 study drug. 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. 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.

In this case, signs and symptoms suggestive of endometrial cancer appeared prior to treatment with mirabegron, suggesting that the cancer was a preexisting condition.

Subject 1597-7875: Left Breast Cancer: The subject is a 61 year old white US female randomized to mirabegron 100 mg on 4 March 2009. On 2009-03-04, 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 study drug. The medical history is not contributory. 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 (2009-03-03). 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.

In this case, breast cancer was diagnosed after 85 days of mirabegron 100 mg therapy in Study 178-CL-049 and 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 19 March 2009. 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 (2009-05-15). 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 study drug. The medical history included benign prostatic hyperplasia (since 2002-09-01). 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.

In this case, prior to entry into the 178-CL-047 study, the subject had a PSA of 3.49 ng/mL. In Study 178-CL-049, his PSA was noted to be 5.4 units (units and reference range not provided). Prostate cancer was detected after 83 days of mirabegron 50 mg therapy and 54 days of mirabegron 100 mg therapy.

Subject 2262-0172: Endometrial Cancer: The subject is 52 year old white Canadian female randomized to mirabegron 100 mg on 18 December 2008. 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 (2009-06-01). This subject did not participate in previous mirabegron studies.

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 and radiation therapy. 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 (2009-03-25) 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.

In this case, symptoms arose just 87 days after initiating mirabegron, suggesting that the endometrial cancer pre-existed mirabegron therapy.

Subject 3016-1796: Hypopharynx Fibroma: The subject is a 48 year old German female randomized to mirabegron 100 mg on 21 January 2009. 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/ER 4 mg treatment group. The subject received a total of 84 days of study drug. 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 performed on day 293. During the 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.

In this case, a 1 cm hypopharyngeal polyp appeared after 293 days of mirabegron. If this polyp was slow-growing, it is reasonable to assume that the polyp pre-existed mirabegron therapy.

Subject 3016-1952: Lung Neoplasm Malignant: The subject is a 61 year old German female randomized to mirabegron 14 January 2009. 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 (2009-07-07). 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 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.

In this case, metastatic squamous cell carcinoma of the lung was observed after 89 days of mirabegron 50 mg therapy and 126 days of mirabegron 100 mg therapy. The history of smoking is a likely etiology of the subject's cancer.

Subject 3022-0128: Prostate Cancer: The subject is a 69 year old white German male randomized to mirabegron 100 mg on 10 December 2008. 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 (2009-03-01). 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 (2008-11-27) and 6.64 mcg/L on day 30 (2009-01-08). 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.

In this case, prostate cancer was detected after 44 days of mirabegron 100 mg therapy. The elevated PSA prior to drug exposure also suggests that this tumor was pre-existing. In addition, the pre-existing elevated PSA did not further increase on mirabegron therapy.

3025-2505: Pancreatic Carcinoma: The subject is a 64 year old German male randomized to mirabegron 100 mg on 10 February 2009. 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 (2009-12-29). 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 study drug. 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.

In this case, symptomatic pancreatic cancer occurred on Day 295.

3032-2166: Thyroid Neoplasm: The subject is a 69 year old white German male randomized to mirabegron 100 mg on 7 February 2009. 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 study drug. The medical history included strumectomy (excision of goiter) (1964), hypothyroidism (since 1968) and benign prostatic hyperplasia (since 2007-04-17). The subject 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. 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. Both lobes of the prostate had cold nodules on preoperative scanning. This finding continues to an indication for left lobe thyroid surgery to rule out carcinoma.

In this case," recurrent goiter" presented on Day 263. Histopathology from a partially completed surgery demonstrated recurrent goiter. Further surgery was planned.

Subject 3034-2276: Breast Cancer: The subject is a 71 year old German white female who was randomized to mirabegron 100 mg on 30 January 2009. 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 study drug. The medical history included biopsy of the left breast (benign results) (1997). 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 (2009-05-27) 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 (2009-05-28), 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 (2009-06-16), 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 (2009-07-27 to 2009-09-02).

In this case, a suspected breast cancer was detected on Day 92 of mirabegron therapy.

Subject 3062-2853: Transitional Cell Carcinoma: The subject is a 58 year old French male randomized to mirabegron 100 mg on 18 March 2009. 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 (2010-01-19). This subject previously participated in the 178-CL-046 study and was randomized to the placebo treatment Group. The medical history included urinary bladder polyp (2003). 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 [2009-04-16] and Day 175 [2009-09-08] 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 (2009-10-30) 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 (2010-02). The treatment was to consist of weekly instillations of 81 mg BCG for 6 consecutive weeks.

In this case of transitional cell carcinoma of the bladder, the subject had a urinary tract infection after just 3 days of mirabegron therapy and hematuria on Day 30. The subject also had a history of "bladder polyp".

Subject 3235-2623: Lung Neoplasm Malignant: The subject is a 74 year old Swedish male randomized to mirabegron 100 mg 30 January 2009. 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 (2009-03-25). 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), and bronchitis (since 2009-01).

On day 53, a serious adverse event of lung cancer was reported. A pulmonary x-ray and nuclear magnetic resonance imaging (MRI) performed on unspecified days in 2009-02, and a bronchoscopy performed on an unspecified day in 2009-03 all showed evidence of a tumor. On an unspecified day in 2009-03, 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.

In this case, lung cancer was detected after 55 days of mirabegron treatment. The subject was a smoker with previous treatment of bronchitis with acetylcysteine and terbutaline.

Subject 3013-0077: Breast Cancer: The subject is a 51 year old German female randomized to tolterodine SR 4 mg on 19 November 2008. 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 with sentinel nodes), 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.

In this case, breast cancer was detected on routine mammography after 203 days of mirabegron therapy.

Subject 3020-0298: Breast Cancer: Hamartochondroma Lung: The subject is a 60 year old German female randomized to tolterodine SR 4 mg on 5 February 2009. 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 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.

In this case, a hamartochondroma of the lung was reported in Day 300 of tolterodine therapy. Hamartochondroma is a very slow growing tumor. With regard to the breast cancer diagnosed on Day 293 of mirabegron therapy, there was no prior mammogram described.

Subject 3068-3245: Uterine Leiomyoma: The subject is a 40 year old French female randomized to tolterodine ER 4 mg on 11 March 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 tolterodine SR/ER 4 mg treatment group with the same assigned subject number. The subject received a total of 90 days of study drug. 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 polymyomia 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.

In this case, a large leiomyomatous uterus was diagnosed after approximately 450 days on tolterodine therapy.

Subject 3253-1509: Endometrial Cancer: The subject is a 64 year old white Swedish female randomized to tolterodine ER 4 mg on 9 December 2009. 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 (2009-10-21). 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 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 (2009-11-02). 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.

In this case. endometrial cancer was diagnosed after 296 days of tolterodine therapy.

Summary. Overall, the gender distribution of the 17 neoplasm subjects is 5 male and 11 females which mirrors the gender 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 appears to be no common mechanism that can explain these heterogeneous tumors. There was no signal of tumor formation in preclinical studies. It is unusual that few tumors were noted in the to-be-marketed (50 mg) dose group in Study 178-CL-049, but considerably more tumors were reported at just twice the dose (100 mg).

FDA's Division of Oncology Products (DOP1) provided the following comments in their consult regarding the reported Neoplasms (which is included in the FDA's briefing package):

- The number of neoplasms reported as an SAE was accurately reflected in the Applicant's study report.
- DOP1 agreed with the Applicant's Adjudication Committee's case by case analysis of neoplasms in Study 049. The narratives show that all the serious neoplasms, except for Case 3016-1796 (fibroma), were supported by pathological evidence and cannot be excluded.
- DOP1 noted that the recommended dose for the proposed indication is 50 mg once a day which had the lowest incidence of neoplasms in the three arms of Study 049.
- DOP1 did not recommend pooling of the data from the mirabegron 50 mg and 100 mg groups for the following reasons:
    - The detected neoplasms were heterologous in tissue of origin
    - 5 of 11 neoplasm SAEs in the mirabegron 100 mg group were diagnosed within 12 weeks of study treatment and 2 of 11 were diagnosed between 3-6 months of treatment.
    - The remaining 4 cases, including the fibroma, were found between months 6-12 of the trial giving a comparable time course to the 3 neoplasms found in the tolterodine arm.
- To the best of their knowledge, DOP1 was not aware of a case in which the incidence of neoplasms was found to be responsive to a two-fold increase in drug dose.
- DOP1 did not find a remarkable imbalance in the incidence of malignancies among the four, 12-week Phase 3 trials (which includes a Phase 3, non-NDA study in Japan).
- DOP1 noted no apparent relationship between prior exposure and neoplasm detection in Study 049. The significance of previous exposure to mirabegron, placebo or tolterodine is difficult to estimate.
- DOP1 had no additional comments with regard to the reported imbalance in neoplasms in Study 049 and no further analysis to recommend.

2.3.5.3 Urinary Tract AEs: UTI, Urinary Retention, Urolithiasis

2.3.5.3.1 Urinary Tract Infection

There was a consistent treatment difference in the proportion of UTIs in the mirabegron and tolterodine groups compared with the placebo groups, with a generally similar occurrence across mirabegron dose groups. In the Phase 3 Population, one or more UTI TEAEs was reported by 99/2736 (3.6%) mirabegron subjects, 34/1380 (2.5%) placebo treated subjects and 15/495(3.0%) tolterodine subjects (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 TEAEs was reported in 143/1632 (8.8%) mirabegron subjects (mirabegron 50 mg: 74/812 [9.1%]; mirabegron 100 mg: 69/820 [8.4%]) and 81/812 (10.0%) tolterodine subjects. 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%]). 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 subjects, elderly subjects and subjects with a history of diabetes generally had higher frequencies of UTI; the frequencies were also higher in the mirabegron-treated subjects than in placebo-treated subjects.

The frequency of UTI TEAEs was examined in the subgroup of male subjects according to history of BPH. Although the rates of UTI were generally higher in male subjects with BPH history compared with male subjects 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 subjects are not at increased risk of UTI with mirabegron treatment. In the Phase 3 Population, one or more UTI TEAEs in subjects 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 subjects.

Thus, there appears to be a modestly increased incidence of UTI in mirabegron subjects as compared to placebo.

2.3.5.3.2 Urinary Retention

There were no clinically meaningful differences between treatments groups in mean changes from baseline to any post baseline visit in post-void residual (PVR) volume or in overall categorical shifts from baseline to post baseline PVR volume. PVR measurements were conducted during the development program as a safety endpoint.

There were no differences in AEs of acute retention of urine observed between placebo-treated and mirabegron-treated subjects in Studies 178-CL-047 and 178-CL-074, where subjects at risk for acute retention of urine were not specifically excluded. One subject treated with placebo (Patient No. 178-CL-047, U00021856492) and one subject treated with mirabegron 50 mg (Patient No. 178-CL-046, 3018-1731) reported an SAE of acute retention of urine (LLT). This subject was a 59-year-old male subject treated with mirabegron 50 mg who reported an SAE of acute urinary retention and UTI. This subject was taking tamsulosin. The subject had a transurethral and suprapubic bladder catheter placement for urinary retention. This subject 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%) subjects reported urinary retention based on TEAE criteria alone and 9/4414 (0.2%) subjects had urinary retention based on PVR criteria alone (defined as change from baseline of ≥ 150 mL); none of the mirabegron subjects reported urinary retention based on both TEAE criteria and PVR criteria. In the placebo group, 7/2142 (0.3%) subjects reported urinary retention based on TEAE criteria alone, 10/2142 (0.5%) subjects had urinary retention based on PVR criteria alone. In the tolterodine group, 3/958 (0.3%) subjects reported urinary retention based on TEAE criteria alone, 4/958 (0.4%) subjects had urinary retention based on PVR criteria alone (i.e., change from baseline of ≥ 150 mL) and 1/958 (0.1%) subjects had urinary retention based on both TEAE criteria and PVR criteria.

Thus, the risk of acute urinary retention with mirabegron in short-term studies appears small.

In the EU/NA Long-term Controlled Population, one or more urinary retention TEAE was reported by 2/1632 (0.1%) mirabegron subjects (mirabegron 50 mg: 1/812 [0.1%]; mirabegron 100 mg: 1/820 [0.1%]) and 3/812 (0.4%) tolterodine subjects.

One subject 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) experienced acute urinary retention. The event (Day 184) occurred in association with worsening paresthesia to the lower extremities and worsening urinary incontinence (Days 199). One subject treated with tolterodine reported the TEAE (by LLT) of acute retention of urine. Another subject 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 subject 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.

Thus, the long term use of mirabegron was associated with a small incidence of urinary retention.

2.3.5.3.3 Urolithiasis

There were 3 subjects in the pivotal 12 week studies who experienced the SAE or the AE requiring discontinuation for renal colic. In the Phase 3 Population, one or more urolithiasis TEAEs was reported in 8/4414 (0.2%) mirabegron and 1/2142 (< 0.1%) placebo subjects, with no apparent mirabegron dose response; no subjects 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 subject reported the AE of ureteral calculus.

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.

Thus, in the 3 month pivotal studies, it appears that there is an increased incidence of reported nephrolithiasis in mirabegron subjects especially in the 25 mg group. It is not known if these stones were diagnosed incidentally or secondary to symptoms. While proteinaceous bladder calculus was noted at very high mirabegron doses in preclinical studies, no renal calculi were noted.

2.3.5.4 Hepatotoxicity

Based on preclinical studies, the liver has been identified as a target organ of concern. The following discussion concern hepatic chemistry changes in the three NDA pivotal studies and the long-term safety population.

2.3.5.4.1 Mean Changes in Liver Function Tests in the 12-week, Pivotal Studies

Mean Changes in 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].

Mean Changes in 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].

Mean Changes in Other Hepatic Chemistries:
The mean change from baseline to final visit in ALP (ranging from 0.3 U/L with mirabegron 100 mg 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.

2.3.5.4.2 Mean Changes in Liver Function Tests in the Long Term Controlled Population

Mean Changes in 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 in the **mirabegron 50 mg**, mirabegron 100 mg, and tolterodine groups, respectively [ISS Table 7.1.3.2].

Mean Changes in 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].

Mean Changes in 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.

2.3.5.4.3 Population Shifts in the Liver Function Tests Phase 3 Pivotal Studies

Population Shifts in ALT
In EU/NA OAB 12-week Phase 3 Population, shifts from baseline to the highest post baseline ALT values represented a categorical increase ; defined as low, normal or high, 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 subjects [ISS Table 7.2.2.2].

Population Shifts in 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 subjects [ISS Table 7.2.1.2].

Population Shifts in 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].

2.3.5.4.4 Population Shifts in Liver Function Tests in the EU/NA Long-term Controlled Population

Population Shifts in ALT
In the EU/NA Long-term Controlled Population, 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 subjects [ISS Table 7.2.3.2].

Population Shifts in 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 subjects [ISS Table 7.2.3.2].

Population Shifts in Other Hepatic Chemistries
The frequency of increase from baseline to highest value for ALP, total bilirubin and GGT were generally similar across all treatment groups

Thus, it appears that with prolonged use of mirabegron, the incidence of upward shift of AST and ALT levels remains constant. In both the Phase 3 12-week and Long-term studies the incidence of upward shifts in these hepatic chemistry values were higher for mirabegron than for tolterodine.

2.3.5.4.5 Potentially Clinically Significant (PCS) Criteria in Liver Function Tests in the EU/NA 12-week Phase 3 Population

In the EU/NA OAB 12-week Phase 3 Population, ≤ 5.5% of subjects experienced a hepatic chemistry value that met a PCS criterion; 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 subjects** and **0.7% of placebo subjects** experienced values > 3 x ULN.

Table 26: 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)
	>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

No subject met the PCS criteria for more than one hepatic parameter 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 events was generally at 8 weeks (56 days) or later.

- One or more hepatotoxicity TEAEs was reported by **41/2736 (1.5%) mirabegron**, **17/1380 (1.2%) placebo** and 10/495 (2.0%) tolterodine subjects (Using MedDRA [v12.1] SOC Hepatobiliary and Investigations search terms).

- 3 subjects (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).

- One or more hepatotoxicity TEAEs leading to permanent discontinuation of study drug was reported by **6/2736 (0.2%) mirabegron** and 1/1380 (0.1%) placebo subjects; no (0/495) tolterodine subjects experienced a hepatotoxicity TEAE leading to permanent discontinuation of study drug.

- Hepatotoxicity was reported as a TEAE for 41/2736 (1.5%) mirabegron subjects; placebo: 17/1380 [1.2%]; tolterodine: 10/495 [2.0%]), from laboratory data for 42/2736 (1.5 %) mirabegron subjects (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 subjects (placebo: 5/1380 [0.4 %]; tolterodine: 5/495 [1.0 %]). Hepatotoxicity from laboratory data is defined as any subject meeting the PCS criteria for hepatic laboratory parameters (ALT or AST > 3 x ULN or total bilirubin or ALP > 1.5 x ULN).

Table 27: Hepatotoxicity AEs in the 12-week 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 6.8.2.3, Table 108, Table 7.1.2.2 ISS

2.3.5.4.6 Potentially Clinically Significant Liver Function Test Abnormalities in the 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 (<=1.3%) and similar across treatment groups.

Two subjects ([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 the AST was 605 U/L. The subject 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 subject was then lost to followup.

Table 28: 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 subject (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]. *This subject had ongoing viral hepatitis as an alternate etiology.* No other subject had elevations of ALT, AST and bilirubin combined at various multiples of abnormal levels.

In the EU/NA Long-term Controlled Population:

- One or more hepatotoxicity TEAEs was reported by 36/1632 (2.2%) mirabegron subjects (**mirabegron 50 mg: 17/812 [2.1%]**; mirabegron 100 mg: 19/820 [2.3%]) and 15/812 (1.8%) tolterodine subjects (Using MedDRA [v12.1] SOC Hepatobiliary and Investigations search terms).

- A total of 3 subjects, 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]).

- One or more hepatotoxicity TEAEs leading to permanent discontinuation of study drug was reported by 2/1632 (0.1%) mirabegron subjects (mirabegron 100 mg: 2/820 [0.2%]) and 1/812 (0.1%) tolterodine subjects).

- Hepatotoxicity was reported as a clinical TEAE for **36/1632 (2.2%) mirabegron** subjects (tolterodine: 15/812 [1.8%]), from laboratory data for 37/1632 (2.3%) mirabegron subjects (tolterodine: 14/812 [1.7%]) and both as a clinical TEAE and from laboratory data for 19/1632 (1.2%) mirabegron subjects (tolterodine: 7/812 [0.9%]).

Table 29: Hepatotoxicity Events in the Long-Term Study 178-CL-049

Hepatotoxicity n (%)	**Mirabegron 50 mg N=812**	Mirabegron 100 mg N=820	Total(N=1632) Mirabegron	Tolterodine ER 4 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

Two subjects in the mirabegron development program, presented herein, met Hy's Law by sustaining 3-fold or higher elevations in serum transaminases and 2-fold or higher elevations in serum bilirubin:

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 subject experienced the SAE of Stevens-Johnson syndrome. On day 24, the subject developed nasopharyngitis, and on days 24 and 25, she 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. The subject's liver enzymes rapidly normalized after stopping all medications.

Patient No. 178-CL-049, 3353-1381, a 67-year-old man treated with mirabegron 50 mg, had a 3-fold or more transaminase elevation combined with a 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 subject 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 subject 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 subject was not listed as an SAE.

Both cases appear confounded by concomitant drugs and co-morbid conditions.

In the EU/NA 12-week Phase 3 Population, one mirabegron 25 mg, **one mirabegron 50 mg** and one tolterodine subject reported hepatotoxicity. One mirabegron subject 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). Another mirabegron subject (176-CL-046:3355 -3411: 50 mg) had just contracted hepatitis A. Finally, Patient 3312-3435 in Study 176-CL-046 (50 mg) had increased liver enzymes as an SAE. This subject was on other drugs that may have contributed to the liver toxicity.

Three mirabegron 100 mg subjects in the EU/NA Long-term Controlled Population, reported an SAE of hepatotoxicity (1630-6655, 2037-0516 and 3367-2053). All recovered or are in the process of recovering according to the Applicant. There were three additional subjects in the long term study not reported as SAEs but with adverse events suggestive of hepatotoxicity, including 1 subject in the long-term study, 3353-1381, receiving mirabegron 50 mg and with pre-existing hepatic disease (hepatitis A, B, C). This subject voluntarily withdrew at Day 201. There were two additional cases in the long-term study (Patient No. 178-CL-049, 3051-2649 and Patient No. 178-CL-049, 2044-6398 [both mirabegron 50 mg]) in whom a rise of the ALT and AST to 10 times ULN with return to normal or baseline levels was reported, with no obvious confounding variables.

Two subjects 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, a possible alternative etiology was identified in each case.

One mirabegron 100 mg long term study subject with an allergic history and mild transaminases at baseline had transaminase rises and underwent a liver biopsy. The liver biopsy was described as being compatible with either drug induced hepatic injury or autoimmune hepatitis. Another 100 mg mirabegron long term subject had liver enzyme elevations in association with a hypersensitivity reaction of hemolytic anemia. A final long-term mirabegron subject (100 mg) at end of study had elevation of transaminases and GGT. She had a previous history of transaminasemia.

Most of the cases of hepatotoxicity occurred in the setting of pre-existing liver function abnormalities, confounding medications, or as part of an allergic phenomenon, but there are cases where there were hepatic enzyme elevations in the absence of such phenomena. Mirabegron may be associated with rare instances of hepatotoxicity.

2.3.5.5 Potential for Endocrine Dysfunction

2.3.5.5.1 Effect on Glucose Metabolism Laboratories

Early in development, the potential for glucose dysregulation was raised for mirabegron, a novel beta-3 adrenergic agonist.

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 subjects [ISS Table 6.11.1.2].
- No subject reported a hypoglycemic SAE or hypoglycemic TEAE leading to permanent discontinuation of study drug.
- One or more hyperglycemia TEAEs was reported by 25/2736 (0.9%) mirabegron, 13/1380 (0.9%) placebo, and 3/495 (0.6%) tolterodine subjects.
- 2/1380 placebo subjects (0.1%), 0/432 mirabegron 25 mg subjects, 5/1375 mirabegron 50 mg subjects, 4/929 mirabegron 100 mg subjects and 0/495 tolterodine subjects reported hypoglycemia (ISS Table 6.10.1.2).

In the EU/NA Long-term Controlled Population:

- One or more hyperglycemia TEAEs was reported by 30/1632 (1.8%) mirabegron subjects (mirabegron 50 mg: 16/812 [2.0%]; mirabegron 100 mg: 14/820 [1.7%]) and 13/812 (1.6%) tolterodine subjects.

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 subjects reported a hyperglycemia SAE. In the EU/NA OAB 12-week Phase 3 Population, however, Patient 178-CL-074: 3032-72997 permanently discontinued study drug due to a hyperglycemia TEAE. In the EU/NA Long-term Controlled Population, no subjects reported a hyperglycemia TEAE leading to permanent discontinuation of study drug.

The data from drug interaction studies with metformin appear to demonstrate that combining metformin and YM178 does not result in a clinically relevant pharmacodynamic interaction on fasting plasma glucose (FPG) or HbA1c levels, or on any of the secondary pharmacodynamic parameters measured in that study.

The data suggest that mirabegron 50 mg is not associated with glucose dysregulation.

2.3.5.6 Cardiovascular Safety Including Effect on Vital Signs

Early Phase 1 data indicated that mirabegron, a beta-3 adrenergic receptor agonist, increased heart rate as well as blood pressure. The effect of mirabegron on heart rate and blood pressure are described here:

2.3.5.6.1 Effect on heart rate

In the Phase 1 study 178-CL-031, and in the Phase 1 TQT study, at doses of **50 mg** and 200 mg, mirabegron was associated with maximal mean increases in pulse of **4.0 - 4.1** and 10.3 to 11.8 bpm, respectively at one or more timepoints. The heart rate increases observed with mirabegron, however, were smaller in Phase 3 studies than in the Phase 1 studies.

In the EU/NA OAB 12-week Phase 3 Population, the adjusted mean difference vs placebo for change from baseline in 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.

In subjects who received the proposed mirabegron therapeutic dose of 50 mg in the Phase 3 studies, 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 subjects who received tolterodine, in both the 12-week studies and the long-term study, in both genders. These changes were not as large as those observed in Phase 1.

Categorical increases from baseline in pulse rate, defined as changes in pulse rate of ≥ 2bpm, ≥ 5bpm, ≥ 10bpm and ≥ 15bpm, 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, including the 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 Applicant reports in the EU/NA Long-term Controlled Population, that 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 in **8/812 (1.0%) mirabegron 50 mg subjects**, 5/820 (0.6 %) mirabegron 100 mg subjects and 12/812 (1.5%) tolterodine subjects.

Female subjects demonstrated a generally higher increase in pulse rate compared with male subjects, consistent with the approximately 40% to 50% increased exposure in female subjects, although this finding was inconsistent across treatment groups and AM/PM measurements.

The overall data suggest a greater effect of mirabegron on pulse rate in younger compared with older subjects, 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 subjects < 65 years vs. ≥ 65 years in any treatment group, while in the long-term study, **changes from baseline AM and PM pulse rate were greater in subjects < 65 years of age than in subjects ≥ 65 years of age**. Pulse rate changes in the mirabegron 50 mg and 100 mg groups were similar to the changes observed in the tolterodine group in both age groups. In an additional analysis categorizing subjects into < 45 years, 45 to < 65 years and ≥ 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 subjects receiving mirabegron or tolterodine, with the greatest change generally seen in subjects < 45 years of age in the 12-week studies. This pattern was not discernible in the AM measurements. In the long-term study, a similar trend was observed in the adjusted mean change from baseline for pulse rate.

Overall, the increase in pulse rate in the OAB population in the Phase 3 studies associated with the proposed therapeutic dose of mirabegron 50 mg in Phase 3 was approximately 1 bpm, similar to tolterodine and did not result in more outliers or tachycardia-related AE than observed with tolterodine. The increase in pulse rate secondary to mirabegron appears to be greater in women compared to men, and in younger compared to older subjects. The mirabegron-associated increase in heart rate was greater in the Phase 1 studies than in the Phase 3 studies. A consult from the Division of Cardiovascular and Renal Products is ongoing.

2.3.5.6.2 Effect on blood pressure

In the Phase 1 study 178-CL-077, a TQT study, mirabegron at doses of **50 mg**, 100 mg and 200mg, was associated with mean increases in SBP and DBP of **4.0**, 7.7, 11.6 and **3.7**, 4.1, 7.7 mm Hg, respectively as compared to placebo at hours 3 or 6 post dose . In the Phase 1 Study 178-CL-031, in the first 8 hours post dose in young healthy volunteers, the maximum increases from baseline in SBP and DBP on Day 14 for **mirabegron 50 mg** were **6.3 and 4.8 mmHg**, respectively. In the healthy volunteers, the blood pressure changes were noted at 5 hours on Day 14 of the study. It is to be noted that that peak plasma levels of mirabegron are reached between 3 and 4.3 hours. In **placebo subjects**,

the maximum increases from baseline in SBP and DBP were **2.4 and 2.3** respectively for the same time period post dose.

In elderly subjects, the mirabegron-associated increase in blood pressure in Phase 1 appears less prominent. In elderly subjects, in the first 8 hours post dose the maximum increases from baseline in SBP and DBP were 3.8 and 5.2 mmHg respectively (occurring at 7 and hours post dose respectively). In elderly placebo subjects the maximum increases in SBP and DBP for the same time period were 3.5 and 1.3 mmHg, respectively. While there appeared to be a dose-responsive maximal increase in the blood pressure in the young volunteers, the mean blood pressure maximal changes with increasing mirabegron doses in the elderly were more variable. For example, at 7 hours post dose at the supratherapeutic 200mg dose, the maximal increases in SBP and DBP were 3.9 and 3.7 mmHg respectively versus placebo maximal blood pressure changes of 3.5 and 4.5 mmHg (0.5h post dose) for SBP and DBP respectively, in elderly volunteers.

It is to be noted, however, that when subject blood pressure monitoring was carried out in the Phase 3 protocols, the mirabegron-associated increases were smaller. This may be due to the AM blood pressures being performed prior to breakfast and just before medication dosage (e.g., representing a "trough blood pressure"). With regard to the PM blood pressure measurement, the Phase 3 protocols pre-defined that at least six hours should elapse between the last morning blood pressure measurement and the first afternoon blood pressure measurement. In actual practice this elapsed time period was much longer, thereby possibly missing the peak blood pressure effects of mirabegron as suggested by the results of Studies 178-CL-031 and 178-CL-077.

With these issues in mind, in the 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 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.

TEAEs 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%]) and mirabegron 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 subjects had generally larger changes from baseline 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 Phase 3 data suggested a greater effect of mirabegron on SBP/DBP in younger compared with older subjects, although this finding was inconsistent. No consistent trend of SBP/DBP change was evident in subjects < 65 years of age compared with subjects ≥ 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 subjects ≥ 65 years, while changes in AM/PM DBP were larger in subjects < 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 subjects into < 45 years, ≥45 to < 65 years and ≥ 65 years of age, baseline SBP was higher in older subjects, 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 subjects who received mirabegron, with the greatest change generally seen in subjects < 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 subjects >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 subjects ≥65 years of age.

Summary. Subjects 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 in the 12-week studies and the long-term study, respectively, comparable to tolterodine in both younger and older subjects.

Objective blood pressure decreases and/or hypotension were similar across treatment groups.

To further assess the effect of mirabegron upon blood pressure a consultation was obtained from the Division of Cardiovascular and Renal Products (DRCP) was obtained. The report of their final consultation is included in the background document.

2.3.5.6.2.1 BP Effects with Drugs that Could Be Administered Concomitantly

Solifenacin

Study 178-CL-069 investigated the effects of steady-state mirabegron on the pharmacokinetics of solifenacin, an anti-muscarinic indicated for the treatment of overactive bladder, in health male and female subjects. Co-administration of mirabegron 100 mg once daily increased the Cmax and AUCinf of solifenacin by 23% and 26%, respectively, without any relevant effect on tmax. 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 greater than those observed with mirabegron alone (6.6 bpm).

Tamsulosin

The cardiovascular interaction between mirabegron and tamsulosin were evaluated in Study 178-CL-080. In each treatment arm, there appeared to be no change in SBP, and a small decrease in DBP in the combination dosing group was observed compared to each drug alone. Taken together, the results did 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. There was a higher exposure to tamsulosin following combination treatment of mirabegron and tamsulosin, perhaps related to mirabegron's inhibition of CYPP450 2D6, but this increase in tamsulosin exposures was not reflected in an overt change in safety profile of tamsulosin. Similarly, the reduction of exposure to mirabegron with combination administration of tamsulosin and mirabegron was not reflected by a change in safety profile in mirabegron.

2.3.5.6.3 Effect of Mirabegron on Electrocardiograms (ECGs)

2.3.5.6.3.1 Non-QT related Effects

Excluding the QT interval, there were no trends observed in the ECG intervals across treatments and subgroups in either the pivotal Phase 3 Population or the long-term Controlled Population. There were no consistent trends for ECG abnormalities either, except for mirabegron-related changes due to increased heart rate, and selected arrhythmia, mostly reported as sinus tachycardia.

2.3.5.6.3.2 QT Effects

In the 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 data were reanalyzed 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). A repeat TQT study (178-CL-077) was conducted with 352 subjects. In the overall population (including 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 supratherapeutic 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 supratherapeutic 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, in the overall population, mirabegron did not cause QTcI prolongation at the proposed therapeutic dose of 50 mg or the supratherapeutic dose of 100 mg, a dose which increased Cmax 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 Cmax 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 a subgroup analysis by gender, mirabegron did prolong the QTc interval in female volunteers at the supratherapeutic 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.

Also of note in this 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) was 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 doses, respectively. For female subjects only, the maximum mean differences (90% confidence interval) were 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. These HR effects occur between 5 and 6 hours post-dose which is consistent with the Tmax of mirabegron.

Additional information relevant to the effect of mirabegron on the QT interval includes:

- There was a higher occurrence of maximum QTcF measurements > 450 msec in the mirabegron 200 mg group compared with placebo. QTc measurements

exceeding this threshold occurred with similar frequency in subjects receiving mirabegron 25, 50 and 100 mg and placebo.

- Maximum QTcF values > 450 msec occurred more often in female than male subjects with a comparable frequency in all treatment groups except for mirabegron 200 mg. No differences were observed between male and female subjects in the frequency of maximum change from baseline in QTcF of ≥30 msec.
- Elderly OAB subjects (≥65 years of age) had a higher frequency of maximum QTcF values > 450 msec; however, the frequency of maximum changes from baseline > 30 msec were similar for subjects < 65 years and ≥65 years of age.
- In the EU/NA OAB 12-week Phase 3 Population, the frequency of QTcF values > 450 msec did not differ between treatment groups but was higher in subjects ≥65 years of age (placebo: 26/479 [5.4%]; mirabegron 25 mg: 7/147 [4.8%]; mirabegron 50 mg: 19/473 [4.0%]; mirabegron 100 mg: 15/325 [4.6%]; and tolterodine: 14/172 [8.1%]) compared with subjects < 65 years of age (placebo: 18/776 [2.3%]; mirabegron 25 mg: 7/259 [2.7%]; mirabegron 50 mg: 13/770 [1.7%]; mirabegron 100 mg: 12/518 [2.3%]; and tolterodine: 4/266 [1.5%]) . Across the dose groups, the frequency of change from baseline in QTcF ≥30 msec and < 60 msec was generally higher in subjects ≥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 subjects < 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 subjects ≥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 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 subject in the mirabegron clinical program.

In conclusion:

- *At the proposed therapeutic dose, mirabegron 50 mg did not have a clinically meaningful treatment effect on QTc interval in females or males.*
- *Prolongation of the QT interval was seen for mirabegron in females at a supratherapeutic dose of 200 mg and this treatment effect could be attributed to higher mirabegron exposure in females. A 200 mg dose of mirabegron is associated with an 8.4- and 6.5-fold increased Cmax and AUCtau compared with the proposed therapeutic dose of mirabegron 50 mg.*
- *In OAB subjects, 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 subjects had higher frequency of maximum QTcF values > 450 msec than male subjects.*

2.3.5.6.4 Cardiovascular clinical adverse events

Based on the mirabegron associated increases in blood pressure and heart rate, the relative risk of major adverse cardiovascular events (MACE) was assessed for the Global OAB Phase 2/3 Population. The relative risk for MACE events was determined to be 0.24 (95% CI: 0.02, l.69) for subjects receiving mirabegron compared with placebo.

There were a very small number of MACE events in the program. The 95% CI for comparison between drug and placebo includes 1.0, thus, it is not possible to conclude either improvement or worsening compared to placebo for MACE.

2.3.5.6.4.1 Atrial fibrillation

Based on mirabegron's effect on increasing heart rate, it was important to determine its effect on supraventricular tachycardias. The overall frequency of atrial fibrillation as a 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), slightly higher for mirabegron compared to placebo, and comparable for mirabegron and tolterodine in the Global OAB 12-week Phase 2/3 Population.

From a clinical perspective, the safety database suggests that the effect of mirabegron on atrial fibrillation appears to be either small or non-existent.

2.3.5.6.4.2 Cardiac failure

Based on the mirabegron-associated increases in blood pressure and pulse, it was important to determine the effect of mirabegron on cardiac failure. The number of subjects (and incidences) of cardiac failure as a TEAE in the Global OAB 12-week Phase 2/3 Population, was 14/2142 (0.7%), 4/811 (0.5%), 14/2131 (0.7%), 15/1305 (1.1%), and 5/958 (0.5%) subjects 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 TEAEs were from the higher level term (HLT) of edema not elsewhere classified (NEC) (29/33 subjects 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, TEAEs of CHF based on the SMQ of cardiac failure occurred in 10/812 (1.2%), 6/820 (0.7%) and 9/812 (1.1%) subjects for mirabegron 50 mg, mirabegron 100 mg and tolterodine, respectively. In this study, the majority of cardiac failure TEAEs were from the HLT of oedema NEC (12/16 subjects in the total mirabegron group).

From a clinical perspective, there does not appear to be an effect of mirabegron on cardiac failure.

2.3.5.7 Hypersensitivity Reactions

During the mirabegron clinical development program, 2 events with findings suggestive of drug hypersensitivity reactions 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. The Sponsor used a broad search strategy using prespecified Standardized MedDRA Queries (SMQs) to capture potential hypersensitivity events. The Sponsor employed an independent Expert Committee (2 dermatologists and one allergist/immunologist) to review 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 subjects came from the Global 12-week Phase 2/3 Population, 12 subjects came from the EU/NA Long-term Controlled Population and 2 volunteers came from the Global Phase 1 Population [Tables 4.1, 4.2, 4.3 and 4.4]. One subject had plausible hypersensitivity reactions in a Global 12-week Phase 2/3 Study (178-CL-046) as well as in the EU/NA Long-term Controlled Population and was counted in each population. The 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 30: Plausible Hypersensitivity Reactions to Mirabegron

Hypersensitivity Reactions	**Placebo**	Mirabegron					Tolterodine
		25 mg	**50 mg**	100 mg	200 mg	300 mg	ER 4 mg
All	**2**	3	**8**	21	2	2	6
Possibly related	**1**	1	**4**	17	2	2	5
In 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
In 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 is determined by the expert panel.
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 subject developed anaphylaxis or angioneurotic edema.

Nonimmediate, primarily cutaneous, reactions were noted in 29 subjects (8 in the long term study and 10 in the Phase 3 studies). A total of 14 of these subjects sustained urticaria, 7 sustained a rash, 4 reported pruritis and one reported purpura. Three tolterodine subjects reported rash. Two subjects within the group of non-immediate, primarily cutaneous, reactions developed leukocytoclastic vasculitis (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]).

The role of mirabegron in these two cases of leukocytoclastic vasculitis is unclear, but a causal association is possible.

Non-immediate, primarily noncutaneous, hypersensitivity reactions were noted in 4 subjects - one subject each in the Phase 3 studies (178-CL-046: mirabegron 100 mg: edema) and in the EU/NA long term study (Patient 2037-0516: mirabegron 100 mg: hemolytic anemia and thrombocytopenia). In addition, one subject each in Study 178-CL-044 and Study 178-CL-045 sustained neutropenia and leucopenia, respectively.

Patient P00244 in Study 178-CL-045 (mirabegron 100 mg) reported as having leukopenia on Day 28, also developed urticaria on her legs, and elevations of liver function tests. By Day 35, the subject 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 subject 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, using Kyufu Gold, mirabegron placebo and mirabegron tablet as 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. 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 subject did not have mucous membrane lesions or blisters or skin erosions with positive Nikolsky's sign. While the subject may not have had SJS, a causally associated major hypersensitivity reaction cannot be ruled out.

Mirabegron has been approved for marketing in Japan and postmarketing adverse events have been reported, including one case of erythema multiforme (Manufacturer's Report Number 2011JP008642; initial report dated 12 December 2011),. The patient was an 86 years old Japanese female. On October 14, 2001, the patient began mirabegron 50 mg for OAB. Prior to initiation of 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.

In summary, the incidence of plausible and related hypersensitivity events was higher in mirabegron than placebo treated subjects. There were several cases of note: Two mirabegron subjects had leukocytoclastic vasculitis. One subject (mirabegron 100 mg) sustained hemolytic anemia and thrombocytopenia. There was on case of severe urticaria originally listed as Stephens Johnson Syndrome. An additional subject, 178-CL-049, 1630-6655 exposed to mirabegron 100 had liver biopsy changes compatible with drug induced hepatic injury or autoimmune hepatitis. Mirabegron appears associated with the occurrence of clinically significant hypersensitivity reactions, some of them severe.

3 Postmarket Experience

Mirabegron was approved for marketing in Japan (tradename 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 69,416 in accordance with 21 CFR 312.32. The total number of patients using Betanis is not known. Mirabegron is marketed at the 25 and 50 mg doses in Japan. The recommended dose is 50 mg with the 25 mg dose of mirabegron to be used in patients with moderate hepatic function disorder or patients with severe renal impairment according to the label. Because of demographic differences, the drug exposure is likely considerably higher than in EU/NA subjects. This may make the adverse event profile for mirabegron different than was reported in the pivotal Phase 3 studies submitted in the NDA. Below is a table summarizing postmarketing safety reports as well as brief narratives for selected cases of clinical interest:

Table 31: Summary of Japanese 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
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 rechallenge	Symptoms resolved with dechallenge	History hypertension, BPH
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

Source: Manufacturer reports to IND 69416.

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 21 December 2011, 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 December 22, 2011 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 during the event and was 181 on 27 January 2012.

This case is confounded by pre-existing medical history and recent addition of paroxetine which makes the conclusion of a causal association with mirabegron problematic.

Chest Pain-possible acute coronary syndrome (2011JP007506): This 73 year old male had 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 tizanelin (a muscle relaxant). Eleven 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 V1 to V3. 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.

The patient had a past history of hypertension and the event occurred in association with pyrexia. Both could act as confounders in this case. Nonetheless, a relationship between the event and mirabegron cannot be ruled out.

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.

The event occurred after 6 days of mirabegron treatment, but the patient's advanced age is a confounder. A relationship between mirabegron and the event cannot be excluded.

Chest Pain (2012JP000177): This 82 year old male patient had 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 29 October 2011. On the same date the patient developed chest pain and mirabegron was discontinued 30 October 2011. 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. Solefenacin was resumed. On November 12, 2011, after having resumed mirabegron (date unknown), the chest pain reoccurred. No chest pain was observed at hospital. Mirabegron was discontinued.

Although the chest pain recurred when mirabegron was re-started, the patient had angina pectoris at baseline and coronary angiography showing 50% stenosis of the LAD. Coronary spastic angina was diagnosed. There may be a relationship between mirabegron and the event in this case.

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, however, on naftopidil (an alpha-1 receptor antagonist). On January 6, 2012, the patient developed cardiac failure with weight gain of 5 kg and facial edema. The brain naturetic 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.

Information is insufficient for analysis.

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.

Erythema Multiforme (2011JP008642): Appears to be a duplicate of previous case (2011JP007679)

Serious cutaneous hypersensitivity reactions were noted in the clinical development program.

Finally, it should be noted that some episodes of urinary retention were reported to have occurred in patients taking antimuscarinic agents (a caution in the Japanese label) and some in men with BPH (a caution in the Japanese label).

4 Conclusions

From the Efficacy perspective, mirabegron 50 mg met its primary and secondary efficacy endpoints in Phase 3 studies. In Study 178-CL-074, the only study in which mirabegron 25 mg was included, mirabegron 25 mg met the primary efficacy endpoints, but did not meet the key secondary endpoint. Further analysis of non-key secondary endpoints demonstrated that the 50 mg dose of mirabegron is clinically superior to the 25 mg mirabegron dose.

From the Safety perspective, there was a large amount of safety data collected in the clinical studies. In all, 7325 subjects received mirabegron in the clinical development program. The population demographics did reflect the patient population who would use the drug clinically post-approval. In terms of deaths, serious adverse events, discontinuations due to adverse events, and commonly reported AEs in the mirabegron clinical studies:

- There were 11 deaths in the mirabegron program, including 2 deaths in ongoing Study 178- CL-090. There were five deaths in subjects receiving mirabegron in completed trials. Overall these deaths appear unlikely to be related to mirabegron.

- The incidence of SAEs in the studies was low and comparable between placebo, mirabegron and tolterodine treatment groups. In the OAB 12-week Phase 3 Population, one or more SAEs was reported for 62/2736 (2.3%) mirabegron, 29/1380 (2.1%) placebo, and 11/495 (2.2%) tolterodine subjects, with no apparent mirabegron dose response. 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).

- In the 12-Week OAB Phase 3 population, TEAEs leading to permanent discontinuation were infrequent (mirabegron: 106/2736 [3.9%]; placebo: 45/1380 [3.3%]; tolterodine: 24/495 [4.8%]). The most common AEs leading to discontinuation 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%]).

- In the 12-Week OAB Phase 3 population, TEAEs reported by ≥3.0% of subjects were: hypertension 200/2736 (7.3) of mirabegron subjects versus 105/1380 (7.6%) placebo subjects, nasopharyngitis 94/2739 (3.4%) versus 35/1380 (2.5%), and UTI 83/2736 (3.0%) versus 25/1380 (1.8%) for placebo.

These routinely collected data do not appear to indicate serious risks of mirabegron; however, a number of adverse events of special safety issues exist that raise concerns and these issues require further consideration. These include:

- Increases in heart rate
- Increases in blood pressure
- Liver function test abnormalities
- Urinary tract related AEs
- Neoplasms
- Hypersensitivity reactions

In regard to the effect of mirabegron on **heart rate**, it is clear that mirabegron, a beta-3 adrenergic agonist, increases heart rate. The extent of that increase and its clinical implications remain under discussion. In the Phase 3 studies, at the proposed therapeutic dose of 50 mg once daily, mirabegron was associated with an approximately 1 bpm increase in adjusted mean change from baseline pulse compared to placebo. In contrast, in the Phase 1 study 178-CL-031, and in the thorough QT study, at doses of 50 mg and 200 mg, mirabegron was associated with larger increases in heart rate: maximal mean increases in pulse for 50 mg and 200 mg were 4.0 to 4.1 and 10.3 to 11.8 bpm, respectively, at one or more timepoints. Thus, a discrepancy exists between findings in Phase 1 studies and Phase 3 studies relating to mirabegron's effects on pulse rate.

Similarly, a discrepancy exists between findings in Phase 1 studies and Phase 3 studies relating to mirabegron's effects upon the **blood pressure**. In Phase 1 studies, the placebo-subtracted effect of mirabegron 50 mg on increasing mean maximal systolic BP was approximately 4 mmHg versus approximately 1 mmHg in Phase 3 studies. The reason for this discrepancy may lie in the different methods used to capture blood pressure data in the Phase 1 studies versus in the Phase 3 studies. Alternatively, the discrepancy between Phase 1 and Phase 3 blood pressure data may be a result of differences in patient populations or in study venues. Either way, there does appear to be an effect of mirabegron on increasing blood pressure; which, when coupled with an effect on increasing heart rate, may pose a health risk to OAB patients. The extent of the increase in blood pressure and the clinical relevance of that BP increase, coupled with a heart rate increase, require further careful consideration.

In regard to **liver function test abnormalities**, infrequent reports of significantly increased liver function tests were observed in subjects taking mirabegron. While some of these cases were confounded by co-morbid conditions (e.g., viral hepatitis) or concomitant hepatotoxic drugs, some cases were not confounded. In 2 mirabegron subjects, liver enzyme elevations were observed in association with hypersensitivity reactions. In one case, a liver biopsy showed drug-induced liver injury versus autoimmune hepatitis (although the subject was on possibly confounding drugs). Two subjects met Hy's Law (one with an associated hypersensitivity reaction and one with hepatitis A, B, C). Two mirabegron 50 mg subjects had serum ALT and AST

elevations to 10 times ULN that returned to baseline while on drug. These isolated cases appear to reflect a rare potential for mirabegron to adversely affect liver function.

A small number of **urinary tract related adverse events**, including urinary tract infection, acute urinary retention, and renal colic, also appears to demonstrate a rare potential for mirabegron to adversely affect the urinary tract, perhaps related to infrequently increasing post-void residual urine.

In regard to **neoplasms**, a variety of neoplasms, including malignant tumors, were reported as serious adverse events in a higher incidence in the mirabegron 100 mg group (1.3%) compared to the mirabegron 50 mg group (0.5%) and to the tolterodine group (0.5%) in the EU/NA Long-Term Study. Although there is no pattern to these neoplasms, and no known mechanism whereby mirabegron would have led to tumor formation, whether these data represent a true mirabegron-related effect is still unknown.

It also appears that mirabegron is associated with the rare occurrence of significant **hypersensitivity reactions**. The application contained reports of 7 severe reactions (2 cases of erythema multiforme [post marketing-Japan], (1) Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, (1) hemolytic anemia and (1) possible autoimmune hepatitis). Plausible hypersensitivity reactions, overall, are reported more frequently for mirabegron than for placebo.

Although the safety results from the clinical trials database appear generally reasonable, the special safety concerns, especially the increases in blood pressure and pulse (observed more clearly in Phase 1 than in Phase 3), require additional consideration relevant to their potential negative public health effects. These special safety concerns should be included in the final risk/benefit assessment for mirabegron for treatment of OAB.

The Division of Reproductive and Urologic Products seeks the advice of the Reproductive Health Drugs Advisory Committeee regarding the demonstration of efficacy and safety for mirabegron, a beta-3-adrenoreceptor agonist and new molecular entity, for the treatment of overactive bladder in patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

CLINICAL PHARMACOLOGY

Office of Clinical Pharmacology (OCP)

B

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no post-marketing commitments are indicated for this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

Mirabegron (also known as YM178) Oral Controlled Absorption System (OCAS) is modified release film coated tablet to be available in two dosage strengths of 25 mg and 50 mg. This is a new chemical entity and first-in-class compound as a selective agonist for human beta 3-adrenoceptor (beta 3-AR). It is being developed for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. The proposed dose is 50 mg once daily with or without food. However, a dose of 25 mg is reserved for patients with severe renal or moderate hepatic impairment.

The sponsor conducted 41 studies consisting of 29 Phase 1 and 2 safety and efficacy (Phase 2/3) studies. The Phase 1 studies consist of 6 biopharmaceutics studies and 23 human PK studies including extensive PK/PD modeling and simulation. The efficacy was evaluated in 6 global studies. The primary three studies are 178-CL-046, 047, and 074. In addition to the standard clinical pharmacology studies, the sponsor conducted two thorough QT (TQT) studies (# 178-CL-037 and 077). Additional analysis was performed to evaluate the cardiovascular effects (e.g., blood pressure and heart rate).

In addition to human *in vivo* studies, the sponsor conducted numerous *in vitro* studies using human biomaterials (e.g., microsomes and cell lines) to characterize the drug metabolic pathways, potential drug-drug interaction (DDI), to identify the isoezymes responsible for the metabolism of mirabegron, and transport mechanisms.

Basic PK Information:

While Mirabegron has a chiral center (R and S) the product under review is the R-enantiomer. It should be noted that no chiral inversion was observed *in vivo*. The plasma protein binding is 71%. The drug binds to albumin and alpha-1 acid glycoprotein. Erythrocytes concentration is 2-fold higher than in the plasma (*in-vitro* data). The drug is widely distributed in the body with large volume of distribution of approximately 1670 L. The terminal elimination half life of mirabegron on average is approximately 50 hours.

The time to reach maximum concentration (Tmax) is 3-4 hours. Based on the Biopharmaceutics Classification System (BCS) mirabegron may be considered Class 3 with high solubility and low permeability (final assessment is still under review). The absolute bioavailability is approximately 29% at 25 mg dose and 35% at 50 mg dose (i.e., dose dependent). Also, the bioavailability appears to be higher in females than in males. Overall, the exposure in females is approximately 40% to 50% higher than in males (uncorrected for body weight). Such trend in exposure in females compared in males has been observed in all studies submitted in this NDA.

The absorption is dependent on the fat content of food; the effect is greater following low fat meal than high fat meal. The maximum concentration (Cmax) and the area under the concentration-time curve (AUC) were reduced by approximately 45% and 17% following high fat meal compared to fasting, respectively. However, when low fat meal was consumed, the Cmax was reduced by 75% and AUC was reduced by 51%. This may cause potential day-to-day fluctuation in mirabegron plasma concentration compared to fasting condition.

Irrespective of this unpredictability in mirabegron systemic exposure due to inconsistencies in food contents and the associated dose dependency in bioavailability, the sponsor's proposed label states that the drug may be given with or without food. It should be noted that pivotal Phase 3 studies were conducted irrespective of food consumption.

Metabolism:

Approximately 55% of radioactivity (^{14}C) is recovered in urine and 34% in feces. The drug is extensively metabolized to approximately 10 metabolites. Approximately 25% of dose was excreted unchanged in urine. None of these metabolites appears to be active in reference to 3-AR. There appear to be several metabolic pathways involved in the metabolism of mirabegron. These include dealkylation, oxidation, and glucuronidation, and amid hydrolysis. Also, these pathways involve several enzymes and isoenzymes such as butyrylcholinesterase, uridine diphospho-glucuronosyltransferase (UGT), CYP3A4,

and CYP2D6, and alcohol dehydrogenase. However, CYP3A4 appears to be the primary responsible isoenzyme.

Dose-Exposure and Specific Population:

It appears, in general, that steady state plasma concentrations are reached within 7 days after once daily (QD) dosing. There was no apparent difference in PK in relation to age (18-55 vs. 65-80 years). Cross study analysis reveals that the exposure in Japanese subjects appears to be higher than that of Westerner subjects (Studies 178-CL-41 and 078). Pop PK analysis shows that the exposure appears to be variable with respect of body weight. A similar analysis showed no apparent differences in PK between Caucasians and African Americans.

In patients with mild, moderate, and severe renal impairment the AUC increased by 31%, 66%, and 118% and the Cmax increased by 6%, 23%, and 92% compared to healthy subjects, respectively. In patients with mild hepatic impairment (Child-Pugh Class A) the Cmax and AUC were increased by 9% and 19% and in moderate (Child-Pugh Class B) they were increased by 175% and 65% compared to healthy subjects, respectively. No study was conducted in severe hepatic impairment patients (Child-Pugh Class C). Based on these studies, the sponsor recommends reduction in dose to 25 mg QD in severe renal and moderate hepatic impairment. However, mirabegron is **not recommended** in patients with severe hepatic impairment (Child-Pugh Class C).

Drug-Drug Interaction (DDI) Findings:

The sponsor conducted several *in vivo* and *in-vitro* drug-drug interaction studies to establish the effect of other drugs on the PK of mirabegron and the effect of mirabegron on other drugs.

Ketoconazole, as a potent CYP3A and P-glycoprotein (P-gp) inhibitor, increased the Cmax and AUC of mirabegron by 45% and 81% while rifampin as a potent enzyme inducer reduced the Cmax and AUC by 35% and 44%, respectively. Other tested drugs such as metformin, solifenacin, and tamsulosin had no effect on mirabegron PK.

From the genetic polymorphism perspective, there was no apparent difference in mirabegron exposure between CYP2D6 poor metabolizers and extensive metabolizers. Based on these findings, the sponsor did not conduct study with CYP2D6 inhibitors. Therefore, the sponsor recommends no dose adjustment is needed when the drug is co-administered with CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers.

Mirabegron increased the Cmax and AUC of two CYP2D6 substrates, metoprolol and desipramine. The Cmax and AUC of metoprolol increased by 90% and 229% and of desipramine by 79% and 241%, respectively. This shows that mirabegron is moderate inhibitor of CYP2D6. Therefore, metoprolol or desipramine dose and possibly other CYP2D6 substrates should be adjusted or titrated when coadministered with mirabegron. Depending on the therapeutic index of these drugs caution should be exercised.

In addition, the exposure of tamsulosin (CYP2D6 and CYP3A4 substrates) was increased by 60% when co-administered with mirabegron. Other studies showed that mirabegron has minimal or no effect on other drugs such as: combined oral contraceptives (COC) containing ethinyl estradiol and levonorgestrel or other *in vivo* probes of metabolism such as: solifenacin (CYP3A4 substrates), warfarin (probe substrate for CYP2C9), metformin, and digoxin.

Exposure-Response and Cardiovascular/QT Data (Analysis is on-going):

At the time of writing this section, further analysis of the data in reference to effect on blood pressure is on going by the cardio-renal and the clinical pharmacology team. Based on the preliminary analysis, mirabegron shows concentration dependent increase in systolic blood pressure (SBP) in healthy subjects from Phase 1 studies and specifically in TQT study (Study # 178-CL-077). This analysis is performed in details in joint documents from the cardio-renal and clinical pharmacology team.

As the dose of mirabegron increased from 50 mg to 200 mg, the heart rate increased from approximately 6.7 beats per minutes (bpm) to 17.3 bpm. In addition, the PK/PD modeling showed that heart rate and blood pressure increased with increasing mirabegron plasma concentration, especially in TQT study (178-CL-077).

Based on Emax model, it appears there is a dose separation in micturation frequency and mean volume voided across the dose range of 25mg, 50 mg, and 100 mg equal to 52%, 85%, and 98% of the Emax (maximum efficacy), respectively. However, the exposure-response relationship for incontinence episodes per 24 hours was flat across the 25 to 100 mg doses range. All doses were associated with approximately 26% reduction in the rate of incontinence compared to placebo.

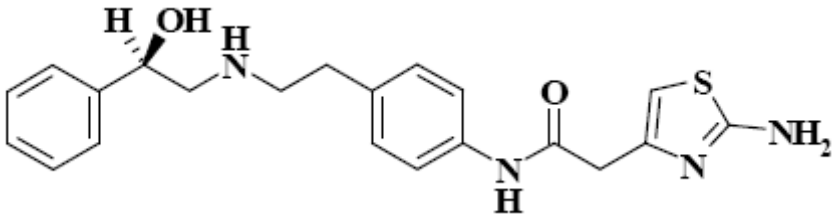
2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Mirabegron (YM178) is a selective agonist for human beta 3-adrenoceptor (beta 3-AR) that is indicated 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 symptoms associated with OAB.

The chemical name is 2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide, the molecular formula is $C_{21}H_{24}N_4O_2S$ and the chemical structure is as follows:



The drug product is formulated as Oral Controlled Absorption System (OCAS) tablets. OCAS is a modified release system (also referred as extended-release or prolonged-release) that allows the release of drug from the tablets for an extended period. The tablets film coated in the dosage strengths of 25 mg and 50 mg. Mirabegron is classified as Class III compound of high solubility and low permeability.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.2.1 Mechanism of Action:

Mirabegron is an agonist of human beta 3-adrenoceptors (AR). It relaxes the detrusor smooth muscle during the urinary bladder fill-void cycle by activation of beta 3-AR without interfering with the voiding contraction.

2.1.2.2.2 Indications:

The proposed indication is for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency

2.1.3 What are the proposed dosage(s) and route(s) of administration?

According to the sponsor's proposed label, the recommended dose of mirabegron is 50 mg orally once daily with or without food. A dose of 25 mg once daily with or without food is recommended in the following populations:

- Severe renal impairment (CLcr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m2)
- Moderate hepatic impairment (Child-Pugh Class B).

Mirabegron should be taken with liquid and swallowed whole. It should not be chewed, divided or crushed.

2.1.4. What are the Core Studies Submitted in this NDA?

The clinical pharmacology program consist of *in vitro* studies that were conducted with human biomaterials and clinical studies to characterize the absorption, distribution, metabolism and excretion (ADME) of mirabegron in healthy volunteers, special populations and subjects with OAB. It also, includes PD studies investigating mirabegron's effects on cardiovascular parameters and intraocular pressure (IOP), and several drug-drug interaction studies.

2.1.4.1 What are the Studies Used Human Biomaterials (*In Vitro* and *Ex Vivo* Studies)?

The sponsor conducted several *in vitro* studies using human biomaterials. The purposes of these studies are to investigate several characteristics including but not limited to the following: permeability, transport, mechanism of hepatic uptake, plasma protein binding, metabolism, effect on cytochrome P450 (CYP) isoforms and transporters, effect of mirabegron on transporters, and chiral inversion.

From all these studies migrabegron was found to be substrate for P-glycoprotein (P-gp), organic cation transporters (OCT 1, 2, and 3) and transported via P-gp. The uptake was saturable. Mirabegron was found weak inhibitory of P-gp and OCT1 and 2. In plasma, the drug binds mainly to albumin and alpha-1 acid glycoprotein.

Mirabegron was found to breakdown to approximately 10 metabolites. Most of these metabolites were <10% of dose which are inactive toward 3AR. The drug undergoes several metabolic pathways including but not limited to the following: oxidation (or *N*-dealkylation) of secondary amine; (2) amide hydrolysis and acetyl conjugation of the amine generated; (3) glucuronidation of the hydroxyl group or the primary amine, or carbamate glucuronidation of the secondary amine; (4) oxidation of the hydroxyl group to carbonyl group. Esterases and in particular butyrylcholinesterase (BChE) are involved in the hydrolysis of mirabegron.

In vitro, mirabegron was found to be a moderate inhibitor of CYP2D6 and a weak inhibitor of CYP3A. These findings were confirmed in *in vivo* human studies with good *in vitro in vivo* correlations using two CYP2D6 substrates, metoprolol and desipramine

and CYP3A substrates using combined oral contraceptives (COC) and solifenacin (see Section 2.4.1.2 effect of mirabegron on other drugs). For metoprolol, the Cmax and AUC were increased by 90% and 229% (Study 178-CL-005) and for desipramine by 79% and 241% (Study 178-CL-058) when co-administered with mirabegron, respectively. There was minimal effect on COC and solifenacin (Study 178-CL-068).

In vitro studies showed no potential DDI between sulfonylurea hypoglycemic agents such as glibenclamide, gliclazide and tolbutamide and mirabegron in both directions. Mirabegron is not an inducer of CYPs. *In vitro* data showed no chiral inversion.

2.1.4.2 What are the Highlights of Studies Conducted in Human (*In Vivo Human* Studies)?

The development of mirabegron involved extensive clinical development and clinical pharmacology programs which consist of 41 studies. The clinical pharmacology Phase 1 program consists of 29 studies as listed below:

- 18 clinical pharmacology studies which used the Oral Controlled Absorption System (OCAS) formulation
- 5 clinical pharmacology studies which used an oral solution or immediate release (IR) solid dosage formulations
- 6 biopharmaceutic (bioavailability, food effect and *In-Vitro-In-Vivo* Correlation [IVIVC]) studies which used OCAS formulations with varying release rates.

In addition, there were 2 thorough QT (TQT) studies (# 178-CL-037 and 077) and PK/PD modeling and simulation reports.

IR formulations of mirabegron were used in the initial studies. Subsequently, the development was focused on modified release formulations leading to the development of mirabegron OCAS. The proposed to-be-marketed formulation of mirabegron is the OCAS medium-release formulation. In this NDA and throughout the review it has also been referred to as “OCAS-M”, “OCAS target” or simply “OCAS”.

The safety and efficacy was evaluated in 6 global, 12 week Phase 2b and Phase 3 studies. The following are the three pivotal efficacy studies in patients with OAB conducted in North America and Europe: 178-CL-046, 047, and 074. The following Sections give the synopsis of the clinical pharmacology studies per subjects:

2.1.4.2.1 PK Studies in Healthy Subjects:

The single- and multiple-dose PK of mirabegron were assessed in several phase 1 studies. Study 178-CL-001, was the first-in-human study of mirabegron given as an IR formulation, was conducted in 2 parts. The first part studied the PK of escalating single doses of mirabegron IR and also assessed dose proportionality of the IR formulation. Part 2 of the study examined the effects of food. Dose proportionality after single and multiple

doses of the OCAS formulation was assessed in several dose escalation studies (178-CL-031, 066, 034, 076, 077, and 072).

In Studies 033 and 076, the PK of mirabegron after intravenous administration was characterized. The mass balance study conducted to determine the disposition of a 160 mg oral dose as solution of ^{14}C-labeled mirabegron in study 007. The effect of food on the PK of IR and OCAS mirabegron formulations has been evaluated in multiple studies. However, the pivotal two studies using OCAS tablets were study 041 in Westerners (conducted in USA) and study 078 in Japanese (conducted in Japan).

2.1.4.2.2 PK Studies in Special Population (Intrinsic Factors Studies):

The sponsor conducted several clinical pharmacology studies to characterize the PK of mirabegron in special populations. These studies include:

Effect Age: The PK in healthy elderly volunteers was examined in studies 178-CL-031 and 072. The effect of age on mirabegron PK was also assessed in an exploratory pooled analysis across phase 1 studies and in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015).

Effect of Gender: Study 072 was dedicated to investigating the PK in healthy male and female volunteers. The effect of sex on mirabegron PK after intravenous and oral administration of mirabegron was examined in Study 178-CL-076. The effect of sex on mirabegron PK was also assessed in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015).

Effect of Race: The influence of race on the PK of mirabegron was explored in the TQT study 178-CL-077. In addition, the effect of race was assessed in an exploratory pooled analysis across phase 1 studies and in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015). Studies178-CL-064, 078, 066 and 034 examined the PK and food effect of single and multiple doses of mirabegron in healthy Japanese volunteers; PK parameters were compared to those obtained in Western volunteers in comparable studies.

Effect Weight: The effect of body weight on mirabegron PK was assessed in a population PK analysis of sparse sampling data obtained in patients with OAB (Study report 178-PK-015).

Genetic Polymorphism: *In vitro* data indicated a minor involvement of CYP2D6 in the metabolism of mirabegron (Study 178-ME-002). The PK in healthy volunteers genotyped and phenotyped as poor (PM) or extensive metabolizers (EM) for CYP2D6 was examined in Study 178-CL-005. In several other studies, genotyping for CYP2D6 was performed. An exploratory pooled analysis was conducted to assess the potential impact of the derived phenotype (i.e. poor, intermediate (IM), extensive or ultrarapid (UM) metabolizer) on the PK of mirabegron.

Renal Impairment: The human mass balance study indicated that mirabegron and its metabolites are substantially eliminated renally (Study 178-CL-007). The PK in volunteers with varying degrees of impaired renal function (mild to severe) was examined in Study 178-CL-038. Subjects with End Stage Renal Disease (ESRD) were not studied. In addition, population PK analysis of sparse sampling data obtained in patients with OAB was used to examine the influence of renal function on the parameters of the models developed (Study report # 178-PK-015).

Hepatic Impairment: *In vitro* and *in vivo* data suggested that mirabegron is cleared through multiple metabolic pathways and possibly biliary excretion of unchanged drug. The PK in volunteers with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment was examined in Study 178-CL-039. Subjects with severe hepatic impairment were not studied.

Drug-drug interaction (DDI) studies were designed based on *in vitro* transporter and metabolism studies and the potential for concomitant use of specific agents with mirabegron.

2.1.4.2.3 Studies of Drug-Drug Interaction-DDI (Extrinsic Factors)

In vitro hepatic oxidative metabolism is primarily mediated by CYP3A4, with a minor role of CYP2D6 (Study 178-ME-002). In addition, mirabegron is a substrate for P-glycoprotein (P-gp) (Studies 178-ME-031, 178-ME-132). DDI studies were performed with ketoconazole, a potent CYP3A and P-gp inhibitor (Study 178-CL-036) and rifampin, a potent CYP3A and P-gp inducer (Study 178-CL-070) to assess the contribution of CYP3A4 to the overall metabolic clearance of mirabegron.

Mirabegron is a moderate inhibitor of CYP2D6 *in vitro* (Studies 178-ME-009, 178-ME-015, 178-ME-068). To evaluate the *in vivo* relevance of these findings, the potential impact of mirabegron on the PK of the probe CYP2D6 substrates metoprolol (Study 178-CL-005) and desipramine (Study 178-CL-058) was assessed. In addition, *in vitro* studies showed that mirabegron is a weak inhibitor of CYP3A at concentrations greatly exceeding those observed *in vivo*. Given the widespread use of combination oral contraceptives (COC) and the fact that the components of the most widely used COC, ethinyl estradiol and levonorgestrel, are substrates of CYP3A4, the effect of mirabegron on the PK of the ethinyl estradiol and levonorgestrel containing COC Minidril® (non-US approved product) was investigated in Study 178-CL-068. The CYP2D6- and CYP3A-inhibitory potential of mirabegron was further explored in interaction studies with the urologic products solifenacin (Study 178-CL-069), which is predominantly eliminated by CYP3A4-mediated metabolism, and tamsulosin (Study 178-CL-080), which is eliminated by CYP2D6- and CYP3A4-mediated metabolism. These studies also assessed the effect of solifenacin and tamsulosin on the PK of mirabegron. In addition, study 178-CL-080 evaluated the potential cardiovascular PD interactions between mirabegron and tamsulosin.

In vitro studies suggested that mirabegron may have weak inhibitory effects on P-gp-mediated drug transport (Study 178-ME-032). The *in vivo* P-gp inhibitory potential of mirabegron was investigated in Study 178-CL-059, using digoxin as a probe P-gp substrate. Other studies were conducted to investigate the potential interactions of metformin, which, like mirabegron, is a renally secreted organic cation (Study 178-CL-006). Given the narrow therapeutic index of warfarin, the effects of mirabegron on warfarin PK, prothrombin time (PT) and International Normalized Ratio (INR) were examined in Study 178-CL-040.

In addition, the potential influence of co-medication on mirabegron PK parameters was tested using population PK analysis of sparse sampling data in patients with OAB (Study Report # 178-PK-015).

2.1.4.2.4 PK Studies in Subjects with Overactive Bladder (OAB)

Population PK analysis methods were used to characterize the clinical PK of mirabegron in subjects with OAB (Study Reports # 178-PK-004, 012, 015). The population analyses included data from subjects enrolled in 3 phase 2 studies (178-CL-008 (IR formulation), 044, and 045) and 4 phase 3 studies (178-CL-046, 047, 048, and 074) that evaluated the efficacy and safety of mirabegron in OAB. The data were derived from sparse sampling strategies used in these studies. Also rich sampling data from healthy subjects were included to help the model development.

2.1.4.2.5 Pharmacodynamic (PD) Studies:

It was observed that mirabegron causes dose-dependent increases in heart rate and blood pressure in healthy subjects. In order to explore the mechanism of the increase in heart rate, a single oral dose of mirabegron was administered before and after beta adrenoreceptor (AR) blockade with the nonselective beta 1/2-AR antagonist propranolol or the selective beta 1-AR antagonist bisoprolol (Study 178-CL-053). The mirabegron associated heart rate effects in the presence of beta-AR blockade were compared to those seen in placebo pretreated subjects. In addition, impedance cardiography (ICG) was used to evaluate the cardiovascular response induced by mirabegron. Initial experience with impedance cardiography was obtained in study 178-CL-072 (see Medical Officer's review).

As mirabegron is a new chemical entity, electrocardiographic assessments, with particular emphasis on QT intervals, were evaluated in the TQT studies 178-CL-037 and 077 (This will be discussed in later sections of this review and for more details please also see Pharmacometric review and QT-IRT review dated January 24, 2012).

A thorough evaluation of the potential for mirabegron to affect intraocular pressure or induce glaucomatous events was conducted. A phase 1b study (Study 178-CL-081) was conducted to address the potential imbalance in glaucoma-type events observed in the mirabegron phase 2/3 clinical program (see medical Officer's review).

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The efficacy of mirabegron in the treatment of patients with symptoms of OAB, including urge urinary incontinence, urgency, and urinary frequency was evaluated in 9 studies including 3 primary phase 3 studies, 1 supportive phase 3 study, 2 supportive phase 2b studies, 1 phase 2a proof-of-concept study, 1 phase 3 active-controlled long-term safety study, and 1 phase 3 open label, long-term safety study.

The focus of this review is on the 3 primary studies (178-CL-046, 047 and 074). It should be noted that of the primary phase 3 studies, only Study 178-CL-074 included mirabegron 25 mg dose. Therefore, the doses studied in Phase 3 are 25, 50, and 100 mg administered daily for 12 weeks.

The efficacy of mirabegron in reducing mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours as compared with placebo was demonstrated across these studies. It appears that all three doses demonstrated superiority compared with placebo. However, there was no much separation between 25 mg and 50 mg doses and 100 mg dose demonstrated slight superiority over 50 mg dose. **Figures 2.2.1.1 and 2.2.1.2** show the mean primary endpoints from studies 074 and 047 as examples.

Figure 2.2.1.1 Mean Incontinence Frequency in Studies 074 and 047
A: Study 074 **B: Study 047**

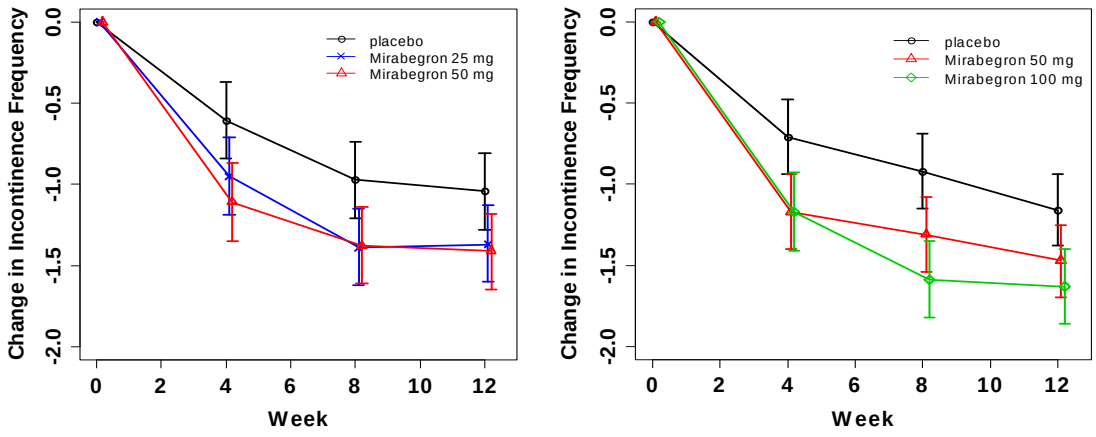
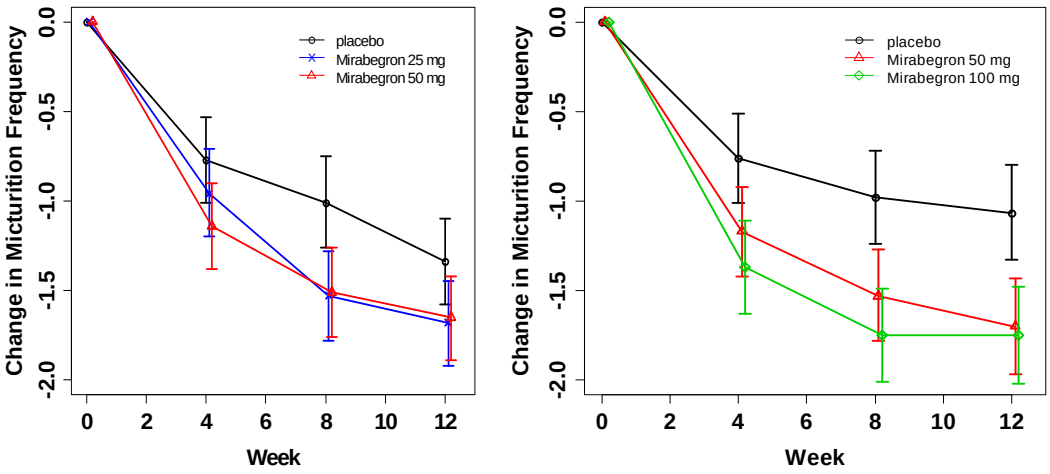
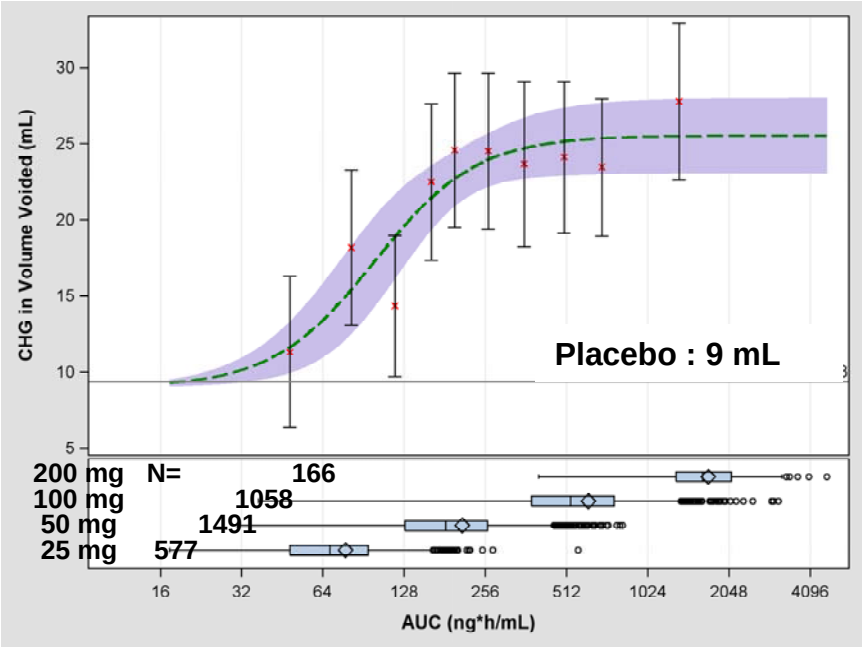


Figure 2.2.1.2. Mean Micturation Frequency in Studies 074 and 047
A: Study 074 **B: Study 047**



The analysis of the data from four Phase 3 studies (178-CL-044, 046, 047, and 074) shows a sigmoid E_{max} shape for exposure-response relationship in reference to volume voided (**Figure 2.2.1.3**). As a secondary efficacy endpoint (i.e., change from baseline to final visit in mean volume voided per micturition), higher mirabegron exposure (i.e. AUC) was associated with larger volume voided. However, doses higher than 50 mg do not seem to offer further advantage. The same conclusion can be reached for the supportive efficacy end point (e.g., number of urgency episodes per 24 hours, the mean level of urgency, and treatment satisfaction-visual analog scale).

Figure 2.2.1.3. Mirabegron Exposure (AUC) –Response Relationship for Volume Voided From for Studies 178-CL-044, 046, 047, and 074.



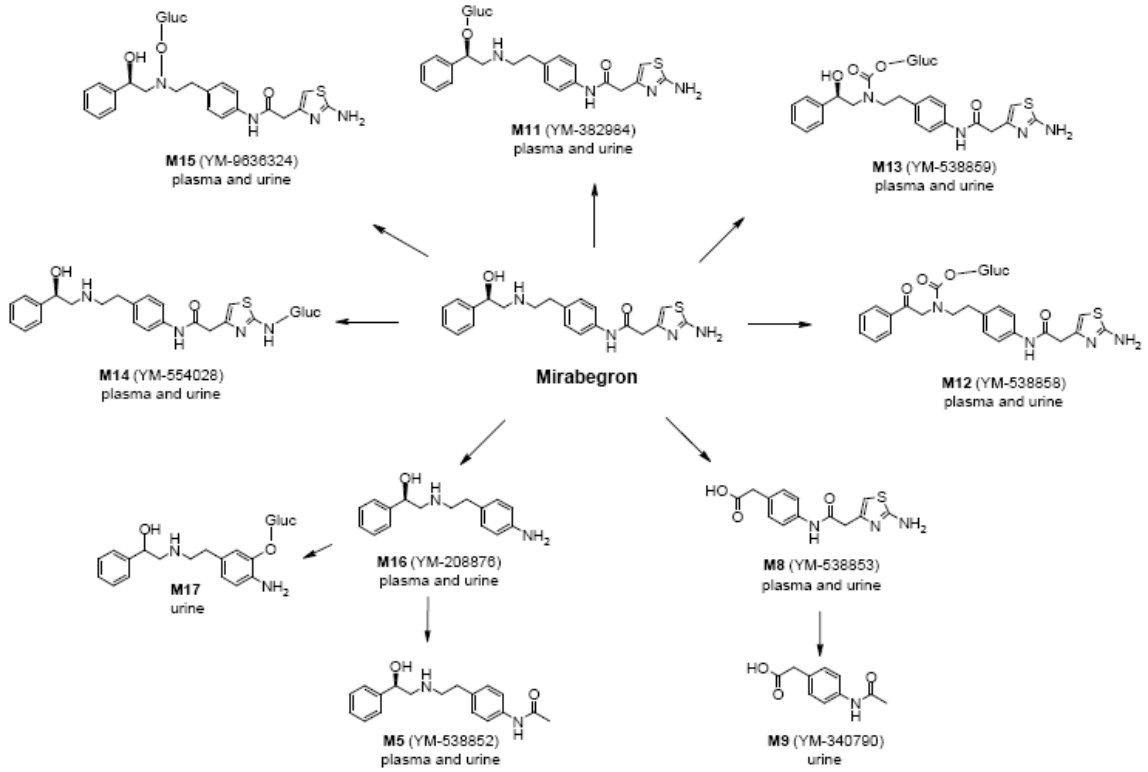
For details of Phase 3 trials and each study, please see the Medical Officer's review. Based on these data, the sponsor's recommended dose is 50 mg daily. However, the 25 mg is reserved for severe renal impairment and moderate hepatic impairment.

2.2.2 What are the Characteristics of Drug Metabolism?

As discussed earlier in this review, mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Urinary excretion data suggest that butyrylcholinesterase is an important enzyme involved in the hydrolysis 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 in the plasma following a single radioactive dose of mirabegron. A total of 10 metabolites (M5, M8, M9, M11, M12, M13, M14, M15, M16 and M17) were identified in human urine. Eight of these (M5, M8, M11, M12, M13, M14, M15, and M16) were also observed in human plasma after oral administration. The postulated metabolic pathways of mirabegron in humans are shown in **Figure 2.2.2.1**.

Figure 2.2.2.1. Metabolic Pathways of Mirabegron in Humans



It should be noted that the metabolite-to-parent AUC ratios were relatively constant across multiple oral doses of 25 to 200 mg QD, indicating that the metabolism of

mirabegron is not saturable over this dose range. The 2 glucuronidated metabolites, M11 and M12, are considered major metabolites which representing 16% and11% of total exposure in plasma, respectively. None of the metabolites observed in plasma were pharmacologically active toward 3AR (see pharmTox review).

Following the administration of 160 mg ^{14}C-mirabegron solution to healthy volunteers (n=4) in a mass balance study, approximately 89% of the administered radioactive dose was recovered: 55% in the urine and 34% in the feces (Study 178-CL-007, **Table 2.2.2.1**). Also, the table shows that 25% of mirabegron dose was excreted unchanged in urine.

Table 2.2.2.1 Summary of Plasma, Blood, Urinary and Fecal PK Parameters of Mirabegron and Total Radioactivity (Study 178-CL-007)

PK parameter (unit)	Plasma Mirabegron	Urine Mirabegron	Plasma Total Radioactivity	Blood Total Radioactivity	Urine Total Radioactivity	Feces Total Radioactivity
t_{max} (hr)	1.00 (0.71)	NA	2.25 (1.44)	2.13 (1.44)	NA	NA
C_{max} (ng/mL)	371 (96)	NA	879 (279)†	777 (211)†	NA	NA
AUC_{inf} (ng·hr/mL)	2285 (250)	NA	10443 (2328)†	13896 (2979)†	NA	NA
$t_{1/2}$ (hr)	47.9 (8.1)	72.9 (13.0)	28.2 (5.4)	30.5 (4.0)	84.5 (11.6)	NA
CL_R (L/hr)	NA	17.7 (2.14)	NA	NA	NA	NA
Ae_{last} urine (%)	NA	25.0 (0.83)	NA	NA	55.0 (2.66)	NA
Ae_{last} feces (%)	NA	NA	NA	NA	NA	34.2 (2.28)

2.2.3 Does this Drug Prolong the QT or QTc Interval?

The sponsor conducted a thorough QT (TQT) study to investigate the effect of mirabegron on the QTc (Study 178-CL-077). The study was conducted in 352 healthy subjects (176 women and176 men) following 10 days daily dosing of 50 mg, 100 mg, 200 mg mirabegron or corresponding each strength placebo and a single oral dose of 400 mg of the active control, moxifloxacin or its placebo. Overall, based on this study mirabegron does not appear to cause QT prolongation at the tested doses. However, a small signal was observed, in female at 200 mg dose.

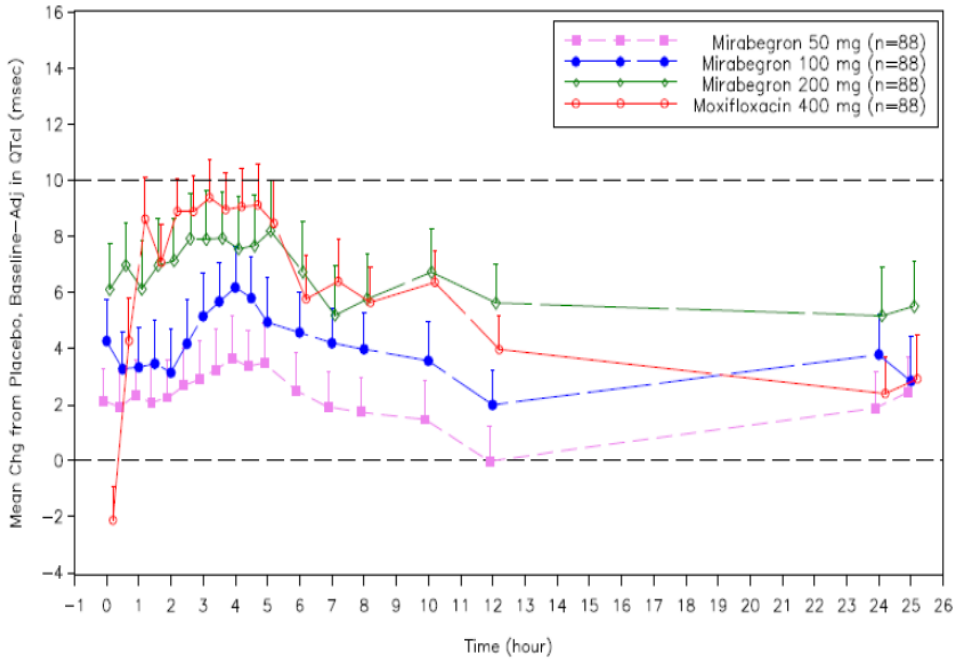
This study was reviewed by the FDA Interdisciplinary Review Team for QT (IRT-QT) in which it was confirmed that there are no major QTc prolongation signals of clinical concern at this time. **Table 2.2.3.1** and **Figure 2.2.3.1** are extracted form IRT-QT review which summarized the QTc data from this study.

Table 2.2.3.1 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Mirabegron and the Largest Lower Bound for Moxifloxacin (FDA Analysis, IRT-QT review dated January 24, 2012))

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Mirabegron 50 mg	4	3.7	(2.3, 5.1)
Mirabegron 100 mg	4	6.1	(4.7, 7.6)
Mirabegron 200 mg	5	8.1	(6.3, 9.8)
Moxifloxacin 400 mg*	3	9.4	(8.1, 10.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.6.

Figure 2.2.3.1 Mean Change in QTc from Placebo for Mirabegron (Study 178-CL-077)



However, it should be noted that throughout this NDA females appear to have higher exposure than males for mirabegron. Overall, the exposure in females is approximately 40% to 50% higher compared to males (**Figure 2.2.3.2** and **Table 2.2.3.2**). This may explains the larger effect of mirabegron on QTc for females. However, based on IRT-QT review, this difference is of no clinical significance at the proposed 50 mg dose.

Figure 2.2.3.2. Mean (± SD) Concentration-Time Profiles of Mirabegron on Day 10, by Gender (Study 178-CL-077)

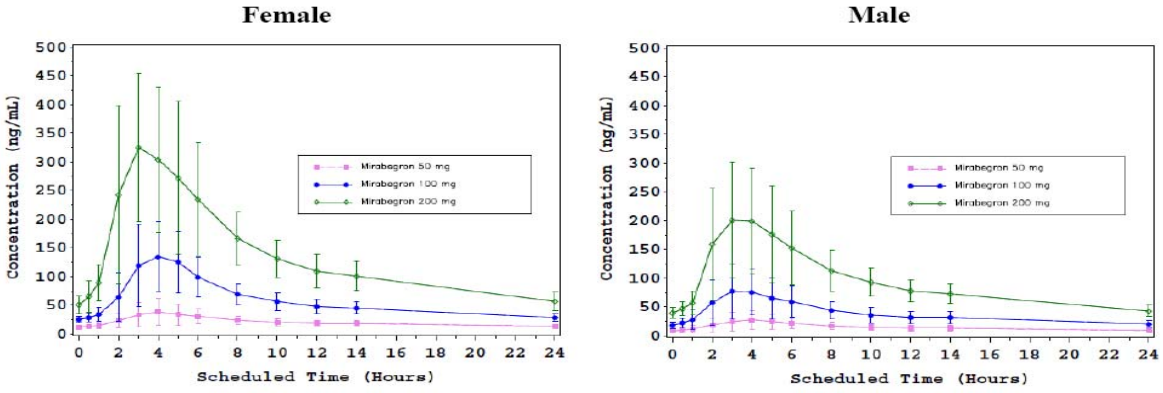


Table 2.2.3.2: Summary of Plasma PK Parameters of Mirabegron on Day 10, by Gender (Study 178-CL-077)

Parameter	50 mg (n=84)		100 mg n=82		200 n=83	
	Female (n= 41)	Male (n=43)	Female (n=41)	Male (n=41)	Female (n=40)	Male (n=43)
AUC (ng.h/ml) (SD)	503.4 (138.42)	361.0 (126.80)	1386.9 (342.53)	916.6 (296.69)	3273.7 (836.52)	2237.0 (586.90)
Cmax (ng/ml) (SD)	47.90 (25.601)	36.20 (17.919)	171.68 (53.927)	105.62 (46.266)	409.21 (139.37)	266.51 (94.420)

It appears that mirabegron increases heart rate 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. The increase in heart rate occurred between 5 and 6 hours post-dose. However, it should be noted that the Cmax of mirabegron occurs between 3 to 4 hours post dose.

The effect of mirabegron on heart rate as well as blood pressure was further analyzed jointly by the Division of Cardio-Renal products and clinical pharmacology team in separate documents (see below summary).

2.2.3.1 Does this Drug Have Effect on Cardiovascular Vital Signs?

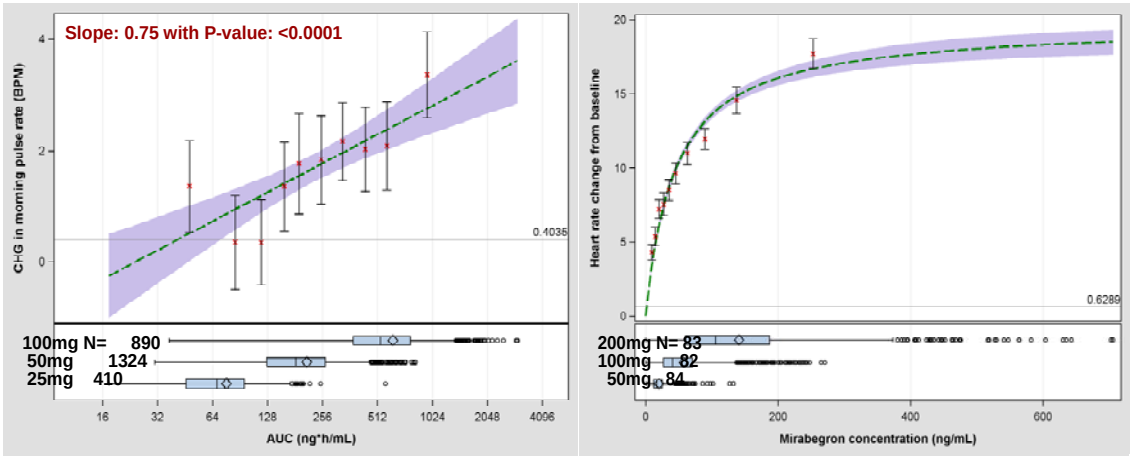
It appears that mirabegron increases blood pressure in healthy subjects as well as heart rate (**Figures 2.2.3.1.1 and 2.2.3.1.1**). These were observed in several studies and further analyzed by the Division of Cardio-Renal Products and by the Office of Clinical Pharmacology, Pharmacometrics Group.

Pharmacometrics Analysis:

As shown from this analysis, higher mirabegron exposure was significantly associated with pulse rate increase in OAB patients (**Figure 2.3.1.1 A**). The heart rate increase with increase in mirabegron plasma concentration in healthy subjects was more pronounced compared to the pulse rate change observed in OAB patients (**Figure 2.2.3.1 B**).

Figure 2.2.3.1.1 Effect of Mirabegron Exposure (AUC) on Pulse Rate and Heart Rate (Data from TQT study 178-CL-077)

A: Pulse Rate[a] **B: Heart Rate[b]**



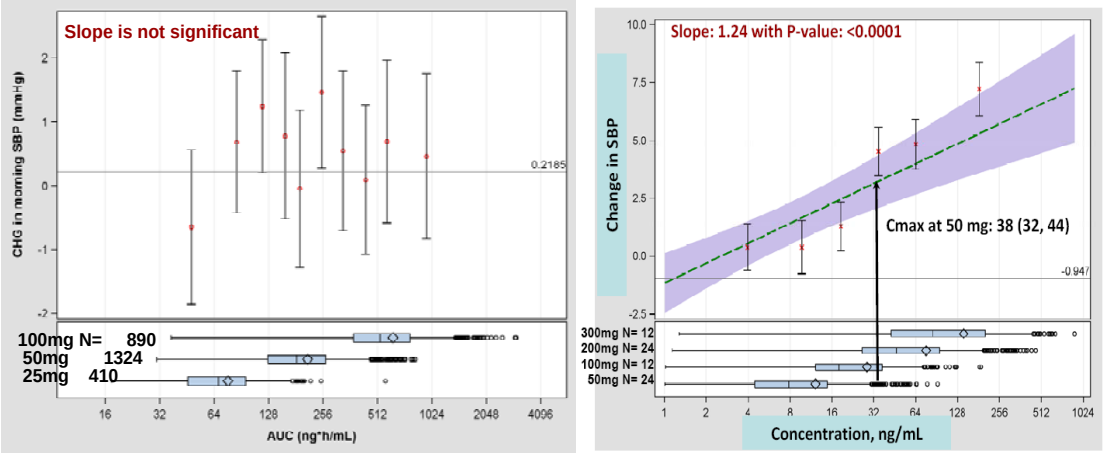
[a]*AUC-pulse rate analysis was conducted in pooled Phase 3 studies (AUC is predicted based on Population PK analysis)*

[b]*Concentration-heart rate analysis was conducted in the TQT study (178-CL-077)*

Analyses of Phase 3 data show no clear relationship between mirabegron exposure (AUC) and systolic blood pressure (SBP) in patients with OAB (**Figure 2.2.3.1.2 A**). However, there was significant increase in SBP with mirabegron plasma concentration in healthy subjects in Phase 1 studies (**Figure 2.2.3.1.2 B**, Study 178-CL-031).

Figure 2.2.3.1.2 Effect of Mirabegron Exposure on Blood Pressure in Phase 3 Trials in OAB Patients and Phase 1 Study 178-CL-031

A: Phase 3 OAB Patients **B: Phase 1[c]**



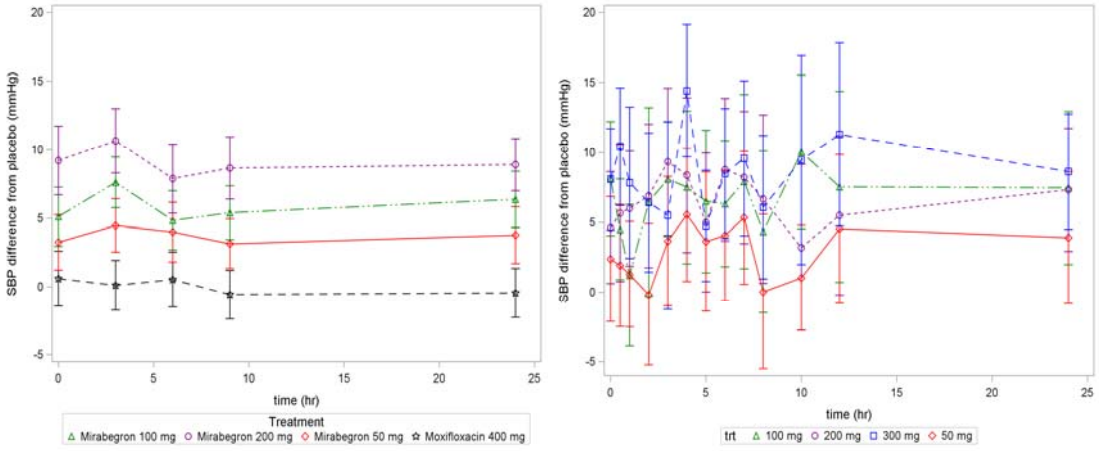
[a]*AUC-SBP analysis was conducted in pooled Phase 3 studies (AUC is predicted based on Population PK analysis)*

[b]*Concentration-SBP analysis was conducted in Phase 1 Study (178-CL-031)*

[c]*For the purpose of plotting, the data are divided in to 6 equal bins of observed mirabegron concentration. The red cross (x) and the associated error bars represent the mean change in systolic blood pressure (SBP) corresponding to the median concentration for each bin and the corresponding 95% confidence intervals. The dashed green line represents regression mean for the entire data and the purple band is the associated 95% confidence interval.*

The effect of dose on SBP data from Phase 1 studies (077 and 031) shows dose proportional increase in SBP at doses of 50, 100, and 200 mg. Correcting the SBP increase for the placebo effect shows that at a dose of 50 mg there is approximately 4 mmHg increase in SBP during 3 to 6 hours after dosing in healthy subjects (**Figure 2.2.3.1.3**).

Figure 2.2.3.1.3 Changed from Placebo of Systolic Blood Pressure (SBP) After Mirabegron 50, 100, and 200 mg Doses in Healthy Subjects in two Phase 1 Studies
A: TQT Study (178-CL-077) **B: Study 178-CL-031**



The potential reasons for observing different exposure-BP relationship between healthy subjects from Phase 1 studies and OAB patients from Phase 2b and 3 studies include:

- Different in population: Healthy subjects from Phase 1 studies are young and have relatively low BP baseline.
- Different in BP measurement: Self measurement of sitting BP in Phase III versus clinic measurements of supine BP in Phase 1 studies.
- Timing of the blood pressure sampling. In Phase 1 studies, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at peak and trough. In the Phase III studies, vital signs were collected by the subject during the AM (after waking up in the morning before the morning dose) and PM (between 2 PM and 6 PM) in a 5-day vital sign diary using a self-measurement device. This sampling scheme did not allow for the assessment of the peak effects which generally occurred around 3 – 4.5 hours coinciding with the peak mirabegron concentrations post-dose.

Based on the Cardio-Renal review, it was concluded that the percentage of patients for change in baseline was higher for systolic SBP and diastolic blood pressure (DBP) after 50 mg dose of mirabegron than for tolterodine, a commonly used anticholinergic drug for the treatment of OAB or placebo. When the data from 50 mg dose is compared to placebo, the differences in final visit categorical SBP/DBP elevation rates are less < 2%.

The effect of mirabegron on SBP/DBP was similar to those of tolterodine. Also, there was a dose response in SBP/DBP effects between 50 mg and 100 mg mirabegron.

Therefore, the cardio-renal team recommends that the sponsor put the target population's characteristics into a Framingham risk model so that they can predict what the likely impact will be on cardio-vascular event rates for the observed blood pressure effects (see cardio-renal review dated January 20, 2012). This comment, among others, was conveyed to the sponsor during the T-con held on February 9th, 2012 and other correspondences during the review cycle.

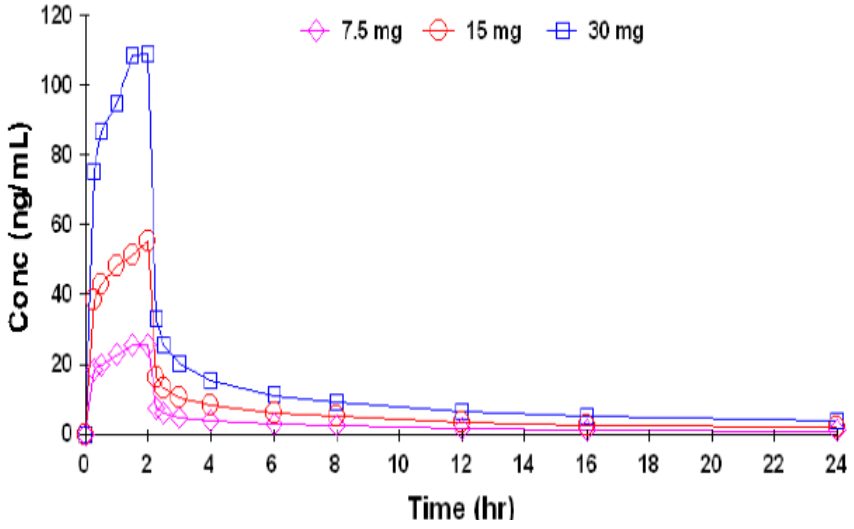
2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of mirabegron and its metabolites? How do the PK parameters change with time following chronic dosing?

The sponsor conducted several studies following single- and multiple-dose to assess the PK profiles of mirabegron. Initially the sponsor conducted PK studies with IR formulation to assess dose proportionality after a single dose escalation (Study 178-CL-001) and after multiple escalating doses (178-CL-002). Later in the development, a dose proportionality studies were conducted with OCAS formulation after single and multiple/repeat dose escalation (Studies 178-CL-031, 066, 034, 076, 072, and 077).

After intravenous (IV) infusion of 7.5, 15, and 30 mg there was no deviation from dose proportionality was observed (**Figures 2.2.4.1.1 and 2.2.4.1.2)** compiled data from two **s**tudies 178-CL-033 and 076). It should also be noted that there was no evidence of deviation from linearity for the dose normalized ratio up to 30 mg. Further, the ratio for females was slightly higher than males. However, the magnitude of difference between females and males after IV infusion appears to be much smaller than that observed after oral administration (see later discussion under effect of gender-sex, **Section 2.3.1.2**).

Figures 2.2.4.1.1: Mean Plasma Concentration-Time Profiles of Mirabegron After IV Infusion to 30 Human Subjects (Study 178-CL-076)



Unlike IV administration, the deviation from dose proportionality was more evident after oral administration. For example, following oral administration of 10 to 340 mg single doses of the IR tablet administered in the fasted state, a greater than proportional increase in mean AUC and Cmax was observed (**Figures 2.2.4.1.3, Study 178-CL-001**). Similarly, greater than dose proportional increase was observed after multiple dose administration of 40 mg to 240 mg doses of IR tablets (Study 178-CK-002).

The same trend was seen in several studies after single doses of 25 mg to 400 mg and repeated administration of 25 mg to 300 mg of OCAS tablets (Studies 178-CL-031, 033, 034, 066, 072, and 077, **Figures 2.2.4.1.4 and 5**).

In terms of steady state concentration, the data from two studies shows it is achieved within 7 days of once daily dosing (Studies 178-CL-031 and 034, **Figure 2.2.4.1.6)**

Figures 2.2.4.1.2: Mean Cmax and AUC of Mirabegron After IV Infusion Over 120 Minutes in 30 Human Subjects From Two Studies: Study 178-CL-076 Doses Were 7.5, 15, and 30 mg Study 178-CL-033 Doses Were 15 mg and 50 mg.

A: Cmax **B: AUC**

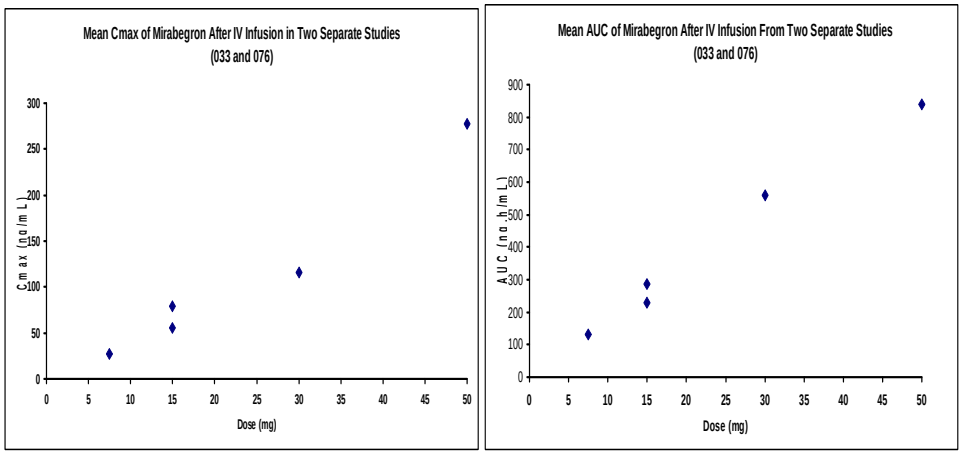


Figure 2.2.4.1.3 Mean (SD) Cmax and AUC of Mirabegron After a Oral Administration of IR Tablets (Study 178-CL-001)

A: Cmax **B: AUC (0-inf)**

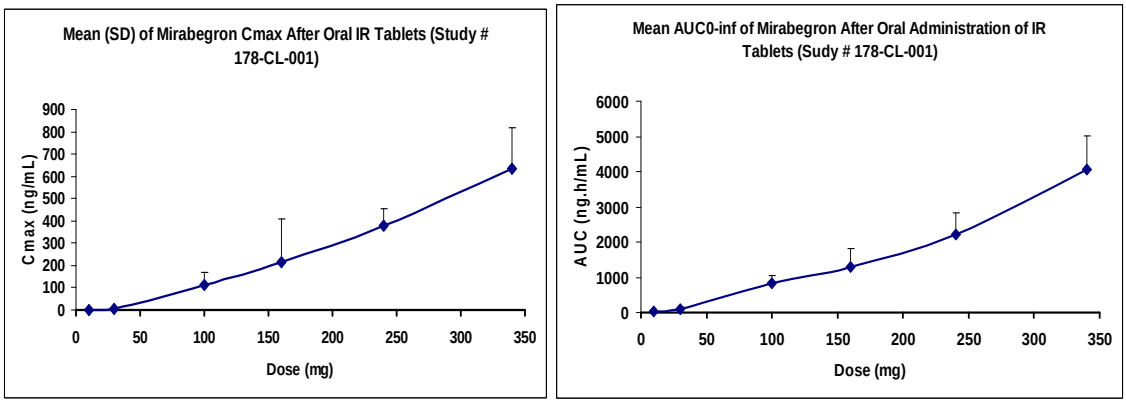


Figure 2.2.4.1.4 Mean Plasma Concentration-Time Profiles of Mirabegron After a Oral Administration of Single Doses of OCAS-M Tables on First Day and Last Day (Study 178-CL-031)

A: First Day **B: Last Day**

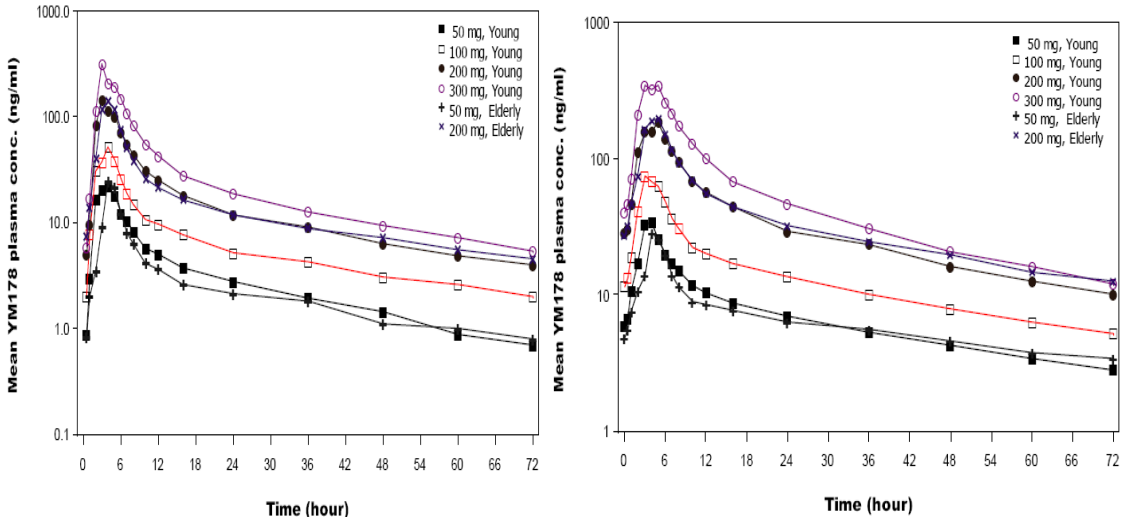


Figure 2.2.4.1.5 Mean (SD) Cmax and AUC of Mirabegron After a Oral Administration of Single and Multiple Doses of OCAS-M Tablets (Study 178-CL-031)

A: Cmax **B: AUC**

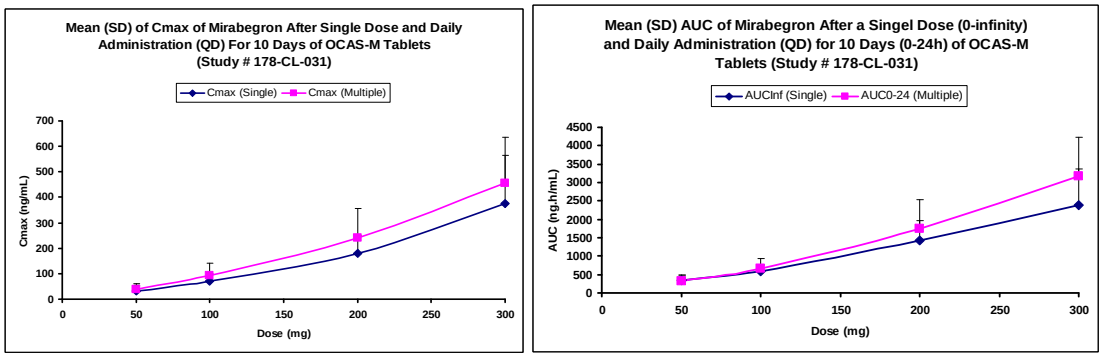
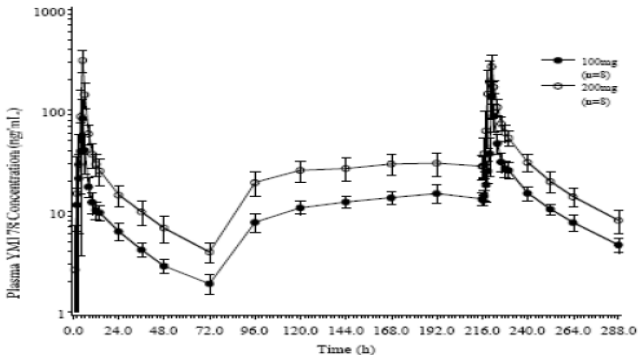


Figure 2.2.4.1.6 Mean Plasma Concentration-Time Profiles of Mirabegron After Single and Multiple Doses in healthy Subjects (Study# 178-CL-034).



Reviewer's Comments:

Overall, after oral administration, a greater than dose-proportional increase in mirabegron Cmax and AUC was observed with increasing dose. These observations are predominantly seen after oral than IV administration and in particular after OCAS tablets. This finding suggests that the observed non-linearity is not related to capacity limited elimination but due to an increase in bioavailability with increasing oral doses (possibly due to an effect on transporters). It should also be noted that a similar trend was observed for mirabegron metabolites (i.e., greater than proportional increase in exposure with increasing dose).

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Effect of Age:

Age has no clinically relevant impact on mirabegron exposure. There were no statistically significant differences in mirabegron Cmax and AUC after multiple doses from 25 mg to 300 mg between subjects over 55 and younger subjects between 18 and 45 years. A pooled analysis across phase 1 studies was conducted using only the treatment arms where mirabegron OCAS was administered alone and under fasted conditions to healthy subjects (**Table 2.3.1.1.1**).

Table 2.3.1.1.1. Across Studies Pooled Analysis for the Effect of Age on Mirabegron PK After Multiple Doses of 50 mg and 100 mg (Study

Dose	Parameter	18-45 years	46-64 years	65-74 years	>75 years
Single Dose					
n		**145**	**18**	**11**	**1**
50 mg	Cmax (±SD) (ng/ml)	33 (35.9)	29.1 (21.8)	32.1 (15.2)	51.5
	AUC (±SD) (ng.h/ml)	340 (237)	314 (165)	308 (79.4)	297
Multiple Dose					
n		**35**	**14**	**19**	**2**
50 mg	Cmax (±SD) (ng/mL)	50.4 (22.3)	58.1 (26.9)	41.7 (19.1)	50.1 (4.24)
100 mg	AUC (±SD) (ng.h/mL)	401 (146)	410 (144)	318 (148)	494 (202)

Reviewer's Comments:

Although the data from this NDA shows no clear trend on the influence of age on any of the PK parameters, population PK analysis showed slight increase (~11%) in mirabegron exposure in subjects with advanced age (Report # 178-PK-015).

2.3.1.2 Effect of Gender:

Overall, mirabegron Cmax and AUC are approximately 40% to 50% higher, respectively, in females compared with males. This increase in exposure appears to be attributed to a higher bioavailability of mirabegron in females compared to males. Based on the overall drug safety and efficacy profiles, the sponsor proposed no dose adjustment is needed in female patients

The study 178-CL-072 was conducted in healthy male and female subjects at doses of 25 mg, 50 mg, and 100 mg QD for 7 days. The data from all three doses were consistent in which the exposure of mirabegron and its metabolites were higher in females than in males.

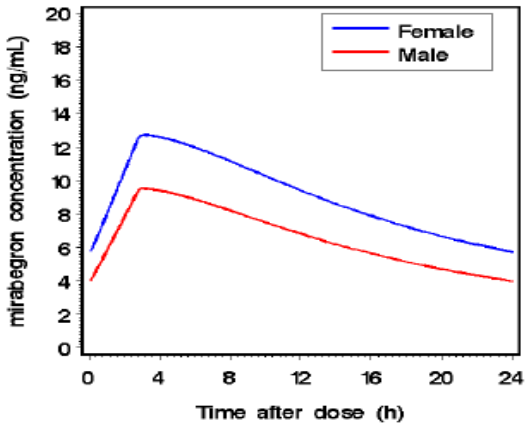
For the 50 mg dose, the ***overall*** mean Cmax and AUC in young or elderly females were numerically higher than that in the corresponding male subjects, the elderly subjects having a more pronounced difference. Specifically, the mean Cmax was 54.4, 58.1 in young males and females and 43.5, and 66.3 in elderly males and females, respectively. For AUC the mean was 413, 471 in young males and females, and 341 and 512 in elderly males and females, respectively. In addition, the half life tended to be longer in females (mean values, 59.0 to 67.9 hr) compared with males (mean values, 56.3 to 60.0 hr).

As described earlier similar results were also obtained in the TQT study 178-CL-077 (**Figure 2.2.3.2**, Section 2.2.3). After multiple doses of 50 mg to 200 mg QD, the AUC was approximately 39% to 51% and the Cmax was approximately 32% to 63% higher in female compared to male volunteers across all doses.

In one of the formulation development study, the sex difference in the PK of mirabegron was shown to be more pronounced after oral administration compared with intravenous administration (Study 178-CL-076). This study was conducted after single IV doses of 7.5 mg, 15 mg or 30 mg of mirabegron. The mean Cmax and AUC were approximately 20% and 27% higher in female subjects compared to male subjects across all dose levels. However, after oral administration of 25 mg, 50 mg or 100 mg of mirabegron, the mean Cmax and AUC were approximately 49% and 64% higher in female subjects compared to male subjects across all dose levels. The absolute bioavailability from this study was 35.0% and 53.0% in females and 24.6% and 40.3% in males at 25 and 100 mg doses, respectively. No differences in bioavailability were observed at the 50 mg dose.

The gender differences in exposure observed in these studies are consistent across studies submitted in this NDA as illustrated from the Pop PK analysis of Phase 2 and 3 data (Report #178-PK-015, **Figure 2.3.1.2.1**). From this analysis, females had a 38% higher AUC than males, although the magnitude of the difference did differ with age and dose as shown above.

Figure 2.3.1.2.1 Influence of Sex on Typical Male and Female Subject's Steady State Plasma Concentration versus Time Profile after Receiving a 50 mg Dose of Mirabegron (Pop PK Analysis, Report #178-PK-015)



Overall, based on the safety and efficacy data in Phase 3 trials and the absence of a significant QT differences in males and females per the QT-IRT analysis and the small difference in effect on blood pressure and heart rate no dose adjustment based on sex is recommended at this time.

2.3.1.3 Effect of Race:

The influence of race on mirabegron plasma exposure was explored in the TQT study 178-CL-077. This study included a similar number of Caucasians and African American subjects. After multiple doses of 50 mg, 100 mg or 200 mg, there were no notable differences in mean Cmax and AUC between Caucasian subjects and African American subjects. The numbers of subjects in other racial categories were too small for an informative analysis.

The influence of race on the PK of mirabegron was further explored in a pooled analysis across phase 1 studies. In this analysis only healthy subjects receiving mirabegron OCAS alone at single or multiple doses under fasted conditions were included. No consistent trend was seen among all treatments between the subjects classified for race. While numerical differences were seen, these differences did not rise to the level of anticipated clinical significance.

Several single-dose and multiple-dose PK studies and food effect studies with mirabegron were conducted in healthy Japanese subjects (178-CL-034, 066, 064 and 078). The food effect study 078 was of similar design as the food effect study 041 performed in Western (i.e. non-Asian) subjects. This allows a direct comparison of single-dose PK parameters between Japanese and Western subjects (**Table 2.3.1.3.1**). Mean Cmax and AUC values in Japanese subjects were approximately 54% to 177% and 42% to 119% higher, respectively, than those observed in Western subjects after single doses of mirabegron (50 mg and 100 mg) under fasted conditions.

This difference in exposure is largely related to differences in body weight. Weight-normalized values for Cmax were about 14% to 64% higher in Japanese subjects compared to those in Western subjects, whereas mean AUC values were 38% higher at the 50 mg dose and 5% lower at the 100 mg dose. Half life was comparable for the Japanese and Western populations, consistent with the comparable degree to which mirabegron accumulated in plasma after once daily dosing in these subjects.

Similar results were obtained after multiple doses of mirabegron. Mean values for Cmax and AUC in healthy young Japanese participants who received mirabegron 100 or 200 mg for 7 days [Study 178-CL-034] were higher compared with healthy young Western subjects who received mirabegron 50 to 300 mg qd for 10 days [Study 178-CL-031]. Mean Tmax and half life values were similar between the 2 populations.

Further analysis of the data between Japanese and Westerners can be seen in the Biopharmaceutics **Section 2.5.3** (Effect of Food).

Table 2.3.1.3.1 Comparison of PK Parameters in Male Japanese and Western Subjects after Single-Dose Administration of Mirabegron

PK parameter	178-CL-078 (Japanese)		178-CL-041 (Western)	
	50 mg n=18	100 mg n=18	50 mg n=17	100 mg n=15
C_{max} (ng/mL)	28.6 (17.3)	89.6 (57.6)	12.8 (5.08)	66.7 (35.8)
Dose and Weight-adjusted C_{max} (ng/mL/(mg/kg))	35.1 (19.2)	58.5 (37.1)	21.4 (8.0)	51.2 (22.9)
AUC_{inf} (ng·hr/mL)	331 (122)	744 (261)	177 (62.1)	668 (270)
Dose and Weight-adjusted AUC_{inf} (ng·hr/mL/(mg/kg))	407 (135)	485 (168)	296 (103)	514 (161)
$t_{1/2}$ (hr)	39.1 (6.7)	34.0 (4.9)	41.5 (7.9)	38.1 (9.3)

Values of PK parameters are mean (SD).

Reviewer's Comments:

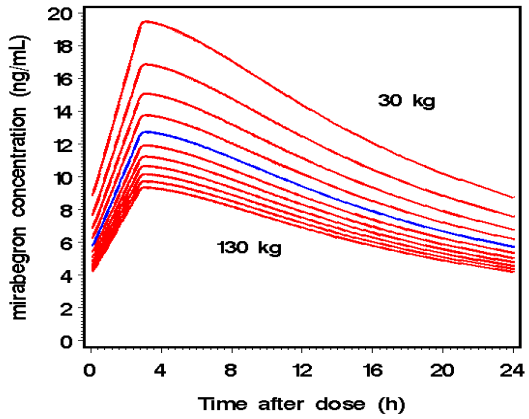
While there is inconsistent trend in exposure between African Americans and Caucasians, there appears to be consistent trend between Japanese and Westerners in that the exposure in Japanese is higher than in Westerners. Based on this data no dose adjustment is necessarily with regards to race and specifically among African Americans and white for mirabegron.

2.3.1.4 Effect of Body Weight:

As described in Section 2.3.1.2 above (i.e., effect of gender), 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.

The influence of weight (including other body size measures such as body mass index, lean body mass and height) has been investigated across a number of population PK analysis using data from healthy subjects and patients with OAB who received IR or OCAS formulations (178-PK-003, 012, 015). In the population PK analysis of phase 2 and 3 data it was shown that body weight affected mirabegron exposure (Study 015). Relative to a subject with a body weight of 70 kg, AUC was about 53% higher in subjects with body weight of 30 kg and approximately 17% lower in subjects with body weight of 100 kg (**Figure 2.3.1.4.1**).

Figure 2.3.1.4.1 Influence of Weight on a Typical Subject's Steady State Plasma Concentration Versus Time Profile after Receiving a 50 mg Dose of Mirabegron (Pop PK analysis 178-PK-015).



Reviewer's Comments:

Based on the data of gender differences, Japanese study, and Pop PK analysis mirabegron exposure appears to be higher in low body weight and surface area than in average weight of 70Kg subjects. Considering the variability in the data and the data from the clinical trials it appears there is no strong safety signal of concern.

2.3.1.5 Effect of Genetic Polymorphism:

It appears that genetic polymorphism for the CYP2D6 isozyme may have little impact on mirabegron exposure. Generic polymorphism was studied as part of the TQT study following 50, 100, and 200 mg doses of OCAS formulation (Study 178-CL-077). At a dose of 50 mg the mean AUC was approximately 30% lower in ultrarapid metabolizers (UM) and 8% higher in PM compared to EM subjects (**Table 2.3.1.5.1**). A similar pattern was also seen for 100 mg and 200 mg. However the number of UMs and PMs was very small in comparison to EMs. It should also be noted that consistent trend of data were also obtained from the pooled analysis of Phase 1 studies.

Table 2.3.1.5.1 Mirabegron PK Parameters in CYP2D6 Phenotyped Subjects After Multiple-Dose Administration in TQT Study 178-CL-077

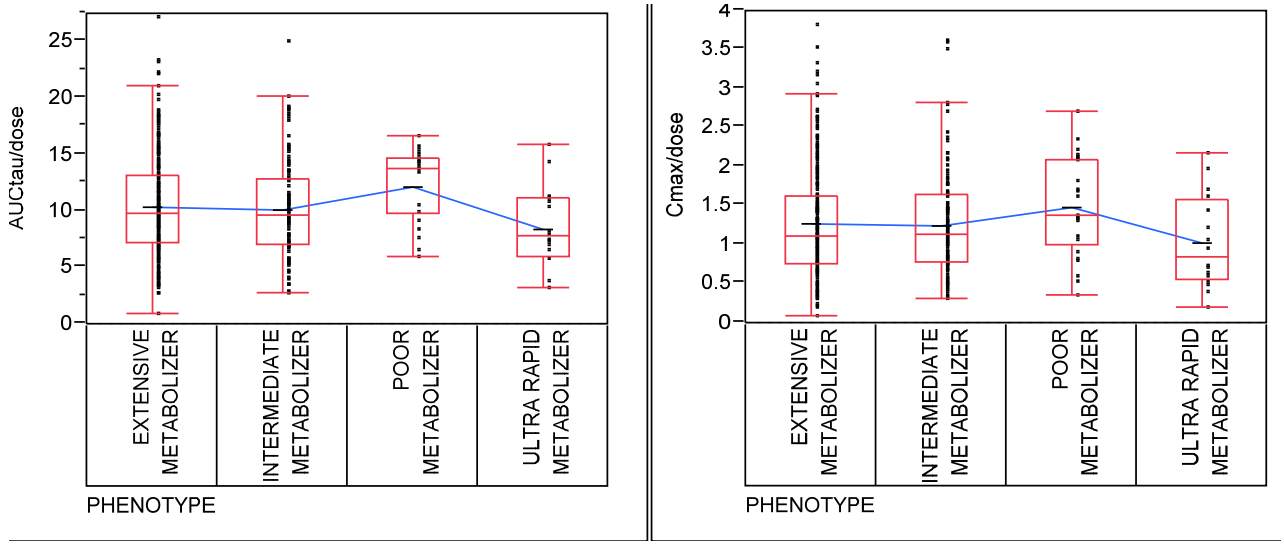
Dose	PK parameter	Predicted CYP2D6 Phenotype				
		UM	EM	IM	PM	INC
50 mg qd	n	5	56	18	3	2
	C_{max} (ng/mL)	30.0 (5.07)	43.0 (26.4)	39.9 (9.87)	43.8 (20.0)	59.0 (17.4)
	AUC_{tau} (ng·hr/mL)	306 (91.7)	438 (167)	417 (89.3)	475 (83.5)	587 (85.1)
	CL/F (L/hr)	182 (77.7)	147 (141)	126 (29.4)	108 (21.0)	86.1 (12.5)
100 mg qd	n	5	43	22	10	2
	C_{max} (ng/mL)	74.4 (48.7)	141 (58.9)	149 (58.1)	147 (63.0)	88.0 (26.3)
	AUC_{tau} (ng·hr/mL)	667 (307)	1170 (375)	1170 (415)	1310 (353)	820 (223)
	CL/F (L/hr)	184 (95.6)	95.4 (37.1)	101 (60.2)	84.0 (33.3)	127 (34.5)
200 mg qd	n	3	62	16	0	2
	C_{max} (ng/mL)	348 (117)	334 (142)	344 (138)	-	274 (37.3)
	AUC_{tau} (ng·hr/mL)	2510 (910)	2760 (949)	2800 (612)	-	1840 (102)
	CL/F (L/hr)	89.5 (40.2)	81.1 (27.2)	75.5 (20.1)	-	109 (6.07)

Values of PK parameters are mean (SD). EM: extensive metabolizer; IM: intermediate metabolizer; INC: inconclusive; PM: poor metabolizer; UM: ultrarapid metabolizer. - : no data.

Further analysis of the data was conducted by the Office of Clinical Pharmacology, Genomics Group to assess the effect of CYP2D6 phenotype on mirabegron exposure. The analysis was conducted by pooling data from three multiple dose studies following OCAS tablets (Studies 178-CL-037, -072, -077). Based on this analysis there was no difference in dose normalized Cmax and AUC among EM, IM, PM, and UM phenotyped individuals (**Figure 2.3.1.5.1**).

Figure 2.3.1.5.1 Variability Chart for Dose-Normalized AUC and Cmax

A: AUC **B: Cmax**



Reviewer's Comments:

The draw back of these analysis is that there is a small number of subjects in UM and PM groups. Collectively, there were no substantial differences in the exposure in any of the groups. Therefore, these results indicate that genetic polymorphism for the CYP2D6

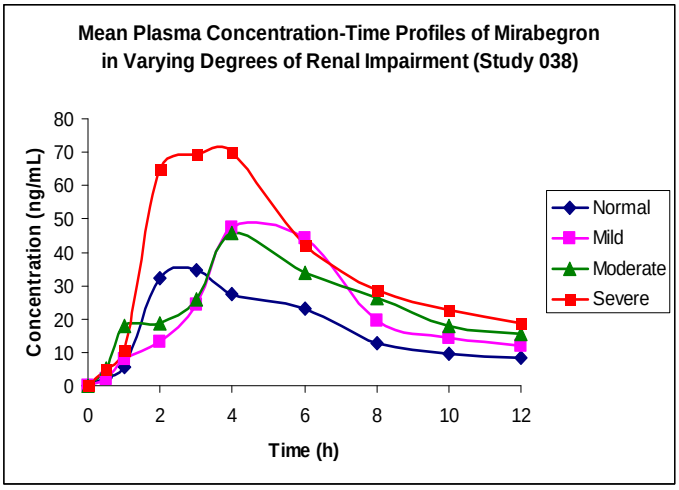
isozyme has little or no clinical impact. The absence of substantial differences in exposure between poor and extensive metabolizers of CYP2D6 is consistent with the multiple elimination pathways for mirabegron.

2.3.1.6 Effect of Renal Impairment

The sponsor conducted a study to characterize the effect of impaired renal function on the single-dose PK of mirabegron (Study 178-CL-038). Mirabegron was administered at a single dose of 100 mg to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m2), mild renal impairment (60 to 89 mL/min/1.73 m2), moderate renal impairment (30 to 59 mL/min/1.73 m2), and severe renal impairment (15 to 29 mL/min/1.73 m2). Subjects with normal renal function were approximately comparable to subjects in the renal impairment groups as regards to age, sex and body mass index (BMI). Subjects with end-stage-renal-disease (ESRD) were not studied.

The plasma exposure of mirabegron was slightly higher in subjects with mild renal impairment (Cmax 6% and AUC 31%) and was noticeably increased in moderate (Cmax 23% and AUC 66%) and severely (Cmax 92% and AUC 118%) impaired subjects relative to those in healthy controls (**Figure 2.3.1.6.1 and Table 2.3.1.6.1 and 2.3.1.6.2**).

Figure 2.3.1.6.1 Mean Plasma Concentration–Time Profiles of Mirabegron in Subjects with Varying Degrees of Renal Function Following Single-Dose Administration of 100 mg Mirabegron



Mean mirabegron elimination half life was slightly increased from approximately 43 h in healthy control to 52 h in severe renal impairment patients.

Renal impairment increased exposure of 8 major mirabegron metabolites, M5, M8, M11, M12, M13, M14, M15 and M16. The extent of exposure was more pronounced in those metabolites that appear to be CYP-mediated such as M8 and glucurinated metabolites such as M14**.** For example, the metabolic ratio (MR) as defined by the metabolite AUC

divided by the parent AUC for M8 and M14 was 13% and 62% in severe group compared to 2% and 16% in normal group, respectively.

Urinary excretion of mirabegron appears to follow the same pattern of the plasma data. The mean cumulative amounts of mirabegron excreted into urine over 120 hours post-dose were similar between the normal and mild groups but was much lower in moderate and severe groups (**Figure 2.3.1.6.2**).

Since mirabegron is extensively metabolized the urinary excretion of unchanged fraction is expected to be small but with similar patterns as that of plasma relative to renal function. Therefore, as expected, the average percentage of unchanged mirabegron excreted in urine was 5.7%, 6.3%, 3.9% and 2.3% of the administered dose in the normal, mild, moderate and severe groups, respectively. From this data it shows that the amount excreted in urine is reduced with the severity of renal function.

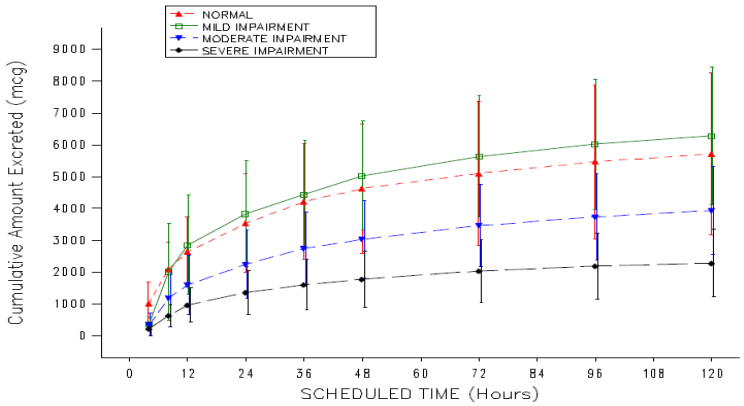
Table 2.3.1.6.1 Mean (SD) Cmax and AUC in Subjects with Varying Degrees of Renal impairment

Parameters	Normal (N=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
Cmax (ng/mL)	45.2 (± 26.94)	57.0 (± 49.99)	60.8 (± 41.95)	93.8 (± 70.12)
AUC (ng.h/mL)	558 (± 249.3)	771 (± 479.6)	992 (± 512.0)	1239 (± 654.2)

Table 2.3.1.6.2 Statistical Analysis of the Effect of Renal Impairment on PK of Mirabegron

Parameter (unit)	Test Group/ Reference Group	Test Group n	Test Group Geometric Mean †	Reference Group n	Reference Group Geometric Mean †	Ratio of Test Group/Reference Group ‡	90% CI for Ratio ‡
AUC_{inf} (hr·ng/mL)	Mild/Normal	8	654.58	8	500.92	130.68	(77.73, 219.69)
	Moderate/Normal	8	832.84	8	500.92	166.26	(98.90, 279.52)
	Severe/Normal	8	1092.77	8	500.92	218.15	(129.76, 366.75)
C_{max} (ng/mL)	Mild/Normal	8	40.39	8	38.12	105.94	(53.36, 210.33)
	Moderate/Normal	8	46.88	8	38.12	122.96	(61.93, 244.12)
	Severe/Normal	8	73.24	8	38.12	192.12	(96.77, 381.43)
AUC_{last} (hr·ng/mL)	Mild/Normal	8	566.76	8	448.40	126.39	(77.09, 207.23)
	Moderate/Normal	8	723.54	8	448.40	161.36	(98.42, 264.56)
	Severe/Normal	8	944.89	8	448.40	210.72	(128.53, 345.49)
CL/F (L/hr)	Mild/Normal	8	152.77	8	199.63	76.53	(45.52, 128.65)
	Moderate/Normal	8	120.07	8	199.63	60.15	(35.78, 101.12)
	Severe/Normal	8	91.51	8	199.63	45.84	(27.27, 77.06)

Figure 2.3.1.6.2. Mean (Standard Deviation) Cumulative Amounts of Mirabegron Excreted Into Urine in Subjects with Varying Degrees of Renal Functions



Based on these data, the sponsor's proposed label is to reduce the dose to 25 mg in patients with severe renal impairment.

2.3.1.7 Effect of Liver Function (Hepatic Impairment)

The sponsor conducted one study in patients with hepatic impairment that were matched to healthy control subjects with respect of sex, age and body mass index (BMI). Two groups of hepatic impairment were studied: mild (Child-Pugh Class A) and moderate Child-Pugh Class B). No patients with severe hepatic impairment (Child-Pugh Class C) were included in this study. All subjects received a single dose of 100 mg mirabegron (Study # 178-CL-039).

Plasma exposure of mirabegron was slightly higher in subjects with mild hepatic impairment, and was increased in moderately impaired subjects relative to those in matching controls (**Figure 2.3.1.7.1**). Mean mirabegron Cmax and AUC were increased by 9% and 19% in mild and 175% and 65% in moderate hepatic impairment relative to subjects with normal hepatic function (**Tables 2.3.1.7.1).** Point estimates and CIs for group comparisons of PK parameters in subjects with varying degrees of hepatic function are presented in **Table 2.3.1.7.2**.

The urinary excretion of unchanged mirabegron slightly increased in patients with hepatic impairment compared to control. The percentage of unchanged mirabegron excreted in urine was about 6.8% of the administered dose in controls, 6.3% in mild, and 9.3% in moderate hepatic impairment. The difference between the normal and moderately impaired hepatic function groups was statistically significant. In addition, plasma concentrations of the eight known metabolites were also increased in both mild and moderate hepatic insufficiency, but as they are considered to be inactive.

From this study it can be stated that there was a substantial increase in systemic exposure relative to that seen for the parent, mirabegron, was observed for 2 of the minor metabolites: the acetylated metabolite M5 and the glucuronide M13.

Reviewer's Comments:

Given its metabolic profile, it would be expected that the exposure of mirabegron would be increased in hepatic impairment patients. Based on these data, the sponsor's proposed recommendation is to reduce the dose to 25 mg once daily in patients with moderate hepatic impairment. However, mirabegron is **not recommended** in patients with severe hepatic impairment (Child-Pugh Class C) as it has not been studied in this population.

Figure 2.3.1.7.1 Mean Plasma Concentration–Time Profiles of Mirabegron in Control and Hepatic Impairment Subjects Following Administration of a 100 mg Dose (Study 178-CL-039)

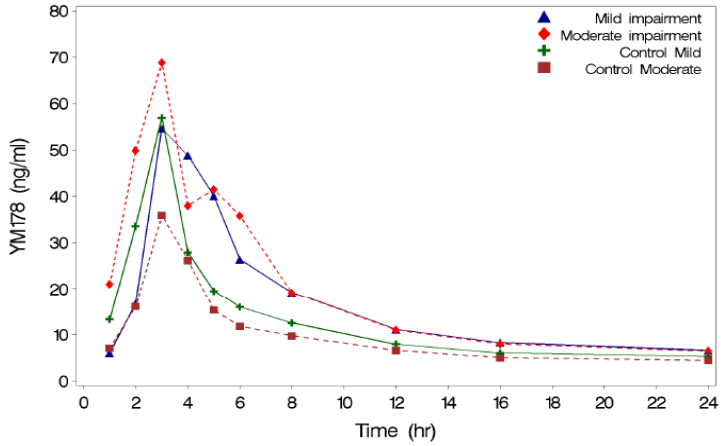


Table 2.3.1.7.1 Mean (SD) Cmax and AUC in Subjects with Varying Degrees of Hepatic Function (Study 178-CL-039)

Parameters	Mild (N=8)	Matching Healthy (n=8)	Moderate (n=8)	Matching Healthy (n=8)
Cmax (ng/mL)	71.9 (± 50.5)	66.9 (± 74.4)	113 (± 68)	41.5 (± 31.8)
AUC (ng.h/mL)	770 (± 391)	615 (± 370)	784 (± 363.0)	486 (± 248)

Tables 2.3.1.7.2 Summary of PK Statistical Analysis (90% CI) of Mirabegron in Subjects with Varying Degrees of Hepatic Function (Study 178-CL-039)

Hepatic Function		Least Square Means[a]			
		Healthy	Impaired	Ratio (Impaired/Healthy)	90% CI
Mild	Cmax) (ng/mL)	46.6	50.7	1.09	0.42, 2.80
	AUC (ng.h/mL)	550	655	1.19	0.69, 2.05
Moderate	Cmax) (ng/mL)	31.7	87.1	2.75	1.08, 6.98
	AUC (ng.h/mL)	424	699	1.65	0.95, 2.85

[a]**Least Square Means do not equal to the arithmetic means in the above table.**

2.4 Extrinsic factors

2.4.1 What extrinsic factors such as drugs influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The sponsor conducted several studies to characterize the effect of other drugs and food on mirabegron PK profiles and also the effect of mirabegron on the PK of other drugs.

Ketoconazole, a potent CYP3A and P-gp inhibitor, causes increase in mirabegron exposure by approximately 45% for Cmax and 80% for AUC (**Table 2.4.1.1,** Study 178-CL-036). However, the co-administration of potent inducers of CYP3A and P-gp such as rifampin, the exposure for mirabegron is decreased by approximately 35% for Cmax and 44% for AUC (**Table 2.4.1.1**, Study 178-CL-070).

Table 2.4.1.1 Effect of Co-administered Drugs on the PK of mirabegron

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

The other significant drug-drug interaction studies in this NDA demonstrating mirabegron is a moderate inhibitor of CYP2D6. In two studies, mirabegron increased the exposure of CYP2D6 substrates such as metoprolol and desipramine. For metoprolol, the exposure was increased by 90% for Cmax and 229% for AUC (Study 178-CL-005) and for desipramine the Cmax was increased by 79% and AUC by 241% (Study 178-CL-058).

Food appears to decrease mirabegron Cmax by 45% to 75% and AUC by 17% to 51%. However, this effect is dependent on the fat contents of food (see Section 2.5, Biopharmaceutics for detail discussion)

The most relevant DDI studies are individually summarized below in this section under two major sub-sections:

A: Effect of other drugs on mirabegron PK
B: Effect of mirabegron on the PK of other drugs

2.4.1.1 What is the Effect of Other Drugs on Mirabegron?

As stated earlier in this review, mirabegron undergoes extensive metabolism with multiple pathways that generates about 10 metabolites. The parent drug and its metabolites are primarily excreted renally and some via biliary excretion. Based on the involvement of multiple metabolic pathways without a single predominant pathway, it can be expected that no single drug may affect the PK profile due to the lack of competition for a particular enzyme.

2.4.1.1.1 What is the Effect of CYP3A and P-gp Inhibitors on Mirabegron PK?

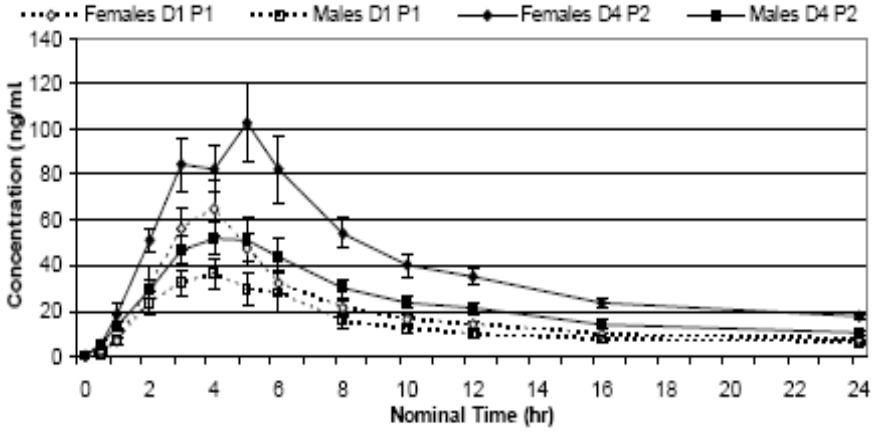
Study 178-CL-036 was conducted to evaluate the effect of ketoconazole as a potent CYP3A and P-gp inhibitor on the PK of mirabegron. In this study, ketoconazole was administered daily at a dose of 400 mg for 9 days prior to the administration of a single dose of 100 mg of mirabegron. The coadministration of ketoconazole resulted in higher mirabegron plasma exposure (45% higher Cmax and 81% higher AUC) than when given alone (**Table 2.4.1.1.1.1 and Figure 2.4.1.1.1.1**).

Table 2.4.1.1.1.1 Mean Cmax and AUC of Mirabegron With and Without Ketoconazole (Study 178-CL-036).

Parameter Gender	LSM† YM178 Alone	LSM† YM178 + Keto	YM178 + Keto/ YM178 Alone‡	90% Confidence Interval‡
AUC_{inf}				
Overall (n = 23)	679.7	1229.6	180.9	[162.6, 201.2]
Females (n = 11)	827.8	1655.0	199.9	[175.2, 228.1]
Males (n = 12)	567.3	936.4	165.0	[139.6, 195.1]
C_{max}				
Overall (n = 23)	57.7	83.7	145.0	[122.5, 171.5]
Females (n = 11)	69.8	115.5	165.5	[128.5, 213.2]
Males (n = 12)	48.5	62.3	128.4	[101.0, 163.1]

†**Least Square Means**

Figure 2.4.1.1.1.1 Mean (± SE) Mirabegron Plasma Concentration-Time Profiles When Administered Alone in Period 1 (P1) and When Administered with After 9 Days of 400 mg Daily Administration of Ketoconazole in Period 2 (P2)



As consistently observed in this NDA, female subjects exhibited higher plasma concentrations compared with male subjects. Mirabegron Cmax and AUC in females in the presence of ketoconazole were increased by 66% and 100% compared to 28% and 65% in males, respectively.

Reviewer's Comments:

The study design was optimal to evaluate the effect of ketoconazole on the PK of mirabegron. From this study, it does not appear that ketoconazole show dramatic effect on the PK of mirabegron.

Considering the safety margins of mirabegron as demonstrated in several clinical trials and TQT study, no dose adjustment is needed when mirabegorn is co-administered with ketoconazole or perhaps other CYP3A inhibitors

2.4.1.1.2 What is the Effect of CYP3A and P-gp <u>Inducers</u> on Mirabegron PK?

The sponsor conducted a study to assess the effect of repeat doses of the potent enzyme and transporter inducer rifampin on the PK of mirabegron and its metabolites. In this study, rifampin was administered daily at a dose of 600 mg for 11 days (Days 5 to 15). Mirabegron was administered on Day 1 (alone) and on Day 12 (with rifampin) as a single dose of 100 mg each time (Study 178-CL-070).

Rifampin decreased mirabegron Cmax by approximately 35% and AUC by 44% (**Figures 2.4.1.1.2.1 and Tables 2.2.1.1.2.1**). In addition, the urinary cumulative excretion of mirabegron was also reduced on Day 12 compared to Day 1 (**Figures 2.4.1.1.2.2).**

The mechanism of this interaction appears to be associated with decrease in the bioavailability of mirabegron when coadministered with rifampin. It should also be noted that due to the enzyme induction, the exposure to mirabegron metabolites was markedly increased and in particular CYP-mediated metabolite M8. Furthermore, rifampin appears to induce the glucuronidation pathways. The exposure of some of mirabegron glucuronides such as M11, M13, and M14 were increased. Other mechanisms may also be involved such as induction of intestinal P-gp efflux as well as some effect on the renal secretion of the metabolites.

Figures 2.4.1.1.2.1 Mean Plasma Concentration-Time Profiles of Mirabegron on When administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)

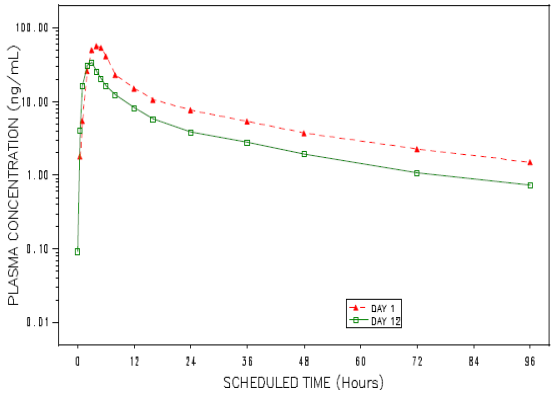
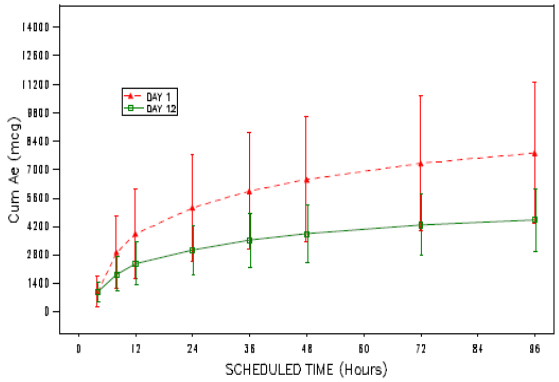


Table 2.4.1.1.1 Statistical Data for Cmax and AUC of Mirabegron When Administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)

Pharmacokinetic Parameter (unit)	Mirabegron Alone		Mirabegron + Rifampin		Ratio‡ (Mirabegron + Rifampin/ Mirabegron Alone)	90% CI of Ratio‡
	n	LS Mean†	n	LS Mean†		
AUC_{inf} (hr·ng/mL)	22	711.10	24	401.42	56.45	(49.07, 64.94)
C_{max} (ng/mL)	24	61.02	24	39.85	65.31	(49.82, 85.62)

Figures 2.4.1.1.2.2 Mean (± SD) Cumulative Amounts of Mirabegron Excreted in Urine When Administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)



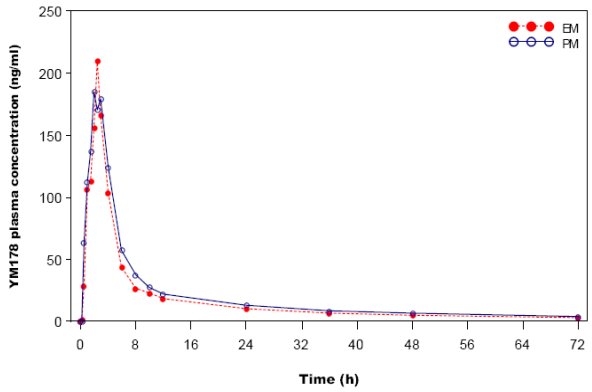
Reviewer's Comments:

Although there was a reduction in mirabegron exposure which is associated with increase in mirabegron metabolites, no dose adjustment is necessary. Since the metabolites are known to be inactive (see PharmTox review), the increase in their exposure may not be of safety concern at this time.

2.4.1.1.3 What is the Effect of CYP2D6 Inhibitors on Mirabegron PK?

As stated earlier the sponsor did not conduct a study to evaluate the effect of potent CYP2D6 inhibitors on the PK of mirabegron. The rationale for this is that CYP2D6 PMs that are considered as a surrogate for CYP2D6 inhibition exhibited similar or only slightly higher mirabegron exposure compared to EMs after a single oral dose of 160 mg mirabegron (**Figure 2.4.1.1.3.1**, Study 178-CL-005). This study will be discussed in more details later in the subsequent Section under "Effect of Mirabegron on Other Drugs-CYP2D6 Substrates/metoprolol).

Figure 2.4.1.1.3.1 Mean Plasma Concentration-Time Profiles of Mirabegron in PMs and Ems of CYP2D6 Following a Single 160 mg Dose of Mirabegron (Study 178-CL-005)



Reviewer's Comments:

The data from this study appears to be convincing that the exposure in CYP2D6 PMs is similar to that of the EMs. This may mimic the inhibition potential of potent CYP2D6 inhibitors.

2.4.1.1.4 What is the Effect of Renally Secreted Drugs on Mirabegron PK?

Interaction with Metformin (Study 178-CL-006):

Like mirabegron, metformin is a renally secreted cation and substrate of OCTs. Therefore, the PK of mirabegron may be altered when co-administered with metformin. Therefore, study was conducted in which metformin was co-administered with mirabegron for 11 days at a 500 mg BID and 160 mg daily dose of mirabegron IR tablets (Study 178-CL-006). The study was placebo controlled.

Mirabegron exposure was only reduced by approximately 20% when co-administered with metformin. It should also be noted that the PK profile of meformin was not affected by the presence of mirabegron.

Reviewer's Comments:

The difference is about 20% reduction in mirabegron Cmax and AUC when co-administered with meformin. This difference may not be of clinical significance. Therefore, no dose adjustment is necessary when mirabegron is co-administered with metformin at therapeutic doses.

2.4.1.1.5 What is the Effect of Other Urologic Drugs on Mirabegron PK?

Interaction with Solifenacin:

Solifenacin is currently marketed by the same sponsor (Astellas Pharma) and was approved in November 19, 2004 for the treatment of over active bladder (NDA 21-518). Study 178-CL-069 was conducted with two main objects:

- To evaluate the effect of steady state concentrations of mirabegron on the single dose PK of solifenacin.
- To evaluate the effect of steady state concentrations of solifenacin on the single dose PK of mirabegron.

The rationale for this study are of two folds:

1. The sponsor is considering development of combination product of solifenacin and mirabigron in the future.
2. Mechanistically, solifenacin is a muscarinic receptor antagonist. Therefore, it is anticipated to inhibits GI motor activity and prolong gastric residence and transit time. From these actions, solifenacin like other muscarnic antagonists, may increase the bioavailability of mirabegron. Furthermore, solifenacin is predominantly metabolized by CYP3A4. This will also assess the competitive interaction with CYP3A4 mediated metabolism with both drugs.

Study Design:

Arm 1: Subjects received a single dose of 10 mg solifenacin on Day 1 and were discharged on Day 9 with washout period until Day 15. Mirabegron was administered daily at a dose of 100 mg as a film coated tablet for 9 consecutive days (Day 15 to Day 23). On Day 9^{th} (Day 23) a single dose of 10 mg solifenacin was administered together with 100 mg daily dose of mirabegron until Day 38.

Arm 2: Subjects received a single dose of 100 mg mirabegron as a film coated tablet on Day 1 with a washout period of 6 days. Solifenacin was administered at a daily dose of 20 mg for 10 consecutive days (Day 7 to Day 16). On the 10th day of solifenacin dosing (Day 16) subjects received a single dose of 100 mg as a film coated tablet of mirabegron together with solifenacin. Solifenacin dosing continued until Day 20^{th}.

The plasma concentration-time profiles and the PK parameters of mirabegron were almost similar when administered alone or in combination with solifenacin. The AUC of mirabegron was increased by 15% when administered with solifenacin. It should be noted

there was minimal effect of mirabegron on solifenacin PK as the Cmax and AUC increased by approximately 23% and 26%, respectively.

Reviewer's Comments:

From this study, it can be concluded that no dose adjustment is necessary for both drugs when concomitantly administered.

Interaction with Tamsulosin:

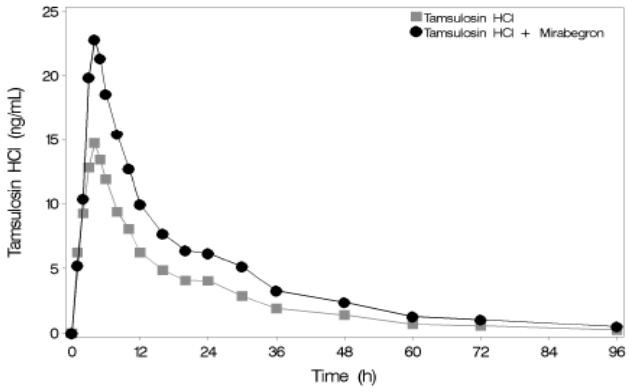
Tamsulosin is an alpha-1 adrenoceptor antagonist for the treatment of benign prostatic hyperplasia (BPH). The rationale for this study is that tamsulosin is eliminated by CYP2D6 and mirabegron is a moderate inhibitor of CYP2D6.

The sponsor conducted a study to investigate the cardiovascular effect and the PK of the mirabegron and tamsulosin when coadministred together (Study 178-CL-080). The study was conducted in 48 healthy males as two arms (n=24 in each arm) as follows:

Arm 1: Single doses of tamsulosin were given alone and after 9 days of dosing with 100 mg doses of mirabegron.
Arm 2: Single doses of mirabegron were given alone and after 5 days of dosing with tamsulosin 0.4 mg doses.

On the day of the combination dose, tamsulosin and mirabegron were administered together. From this study there was no effect of tamsulosin on the plasma concentration-time profiles of mirabegron or its PK Parameters. In terms of effect of mirabegron on tamsulosin PK, there was about 1.6 fold increase in exposure (Cmax and AUC) of tamsulosin (**Figure 2.4.1.1.5.1)**.

Figure 2.4.1.1.5.1. Mean Plasma Concentration Time Profiles of Tamsulosin Single Dose and Combination Dosing with Mirabegron – Treatment Arm 1 (Study 178-CL-080)



Reviewer's Comments:

From this study the effect of tamsulosin on mirabegron PK was minimal as the Cmax and AUC decreased by approximately 15%. However, mirabegron increased the exposure of

tamsulosin by approximately 1.6 fold. Overall, there is no need for dose adjustment when mirabegron and tamsulosin are administered together.

2.4.1.2 What is the Effect of Mirabegron on Other Drugs?

Based on *in vitro* DDI studies and the potential for predicting *in vivo* drug interaction, several studies were conducted to evaluate the effect of mirabegron on other drugs that are likely to be co-administered with mirabegron. These studies are briefly described below:

2.4.1.2.1 Studies with CYP2D6 Substrates:

Two studies were conducted using two known CYP2D6 substrates: metoprolol (Study 178-CL-005) and desipramine (Study 178-CL-058).

Metoprolol (Study 178-CL-005):

As described in the previous Section, this study was conducted into two parts: one part to compare the PK of mirabegron in CYP2D6 PM and EM subjects and the second part was to evaluate the effect of multiple doses of mirabegron on the PK/metabolism of metoprolol as a model substrate for CYP2D6. The focus of this Section is on the second part.

This was a cross-over design, in 12 healthy male subjects genotyped and phenotyped as EM for CYP2D6. Each subject received a single 100 mg dose of metoprolol tartrate as a model substrate on the first day of dosing (Day 1). After a 1-day washout mirabegron 160 mg IR tablet was given alone and once a day for 4 days (Days 3-6) and in combination with metoprolol tartrate 100 mg for 1 day (Day 7). The PK profile of metoprolol tartrate was assessed on the first day and on the last day of dosing. Plasma concentrations of mirabegron were measured on the last day of monotherapy and during the combination treatment of mirabegron with metoprolol tartrate.

From this study there was a marked increase in the plasma concentration-time profiles of metoprolol when coadministered with mirabegron (**Figure 2.4.1.2.1)**. The mean Cmax and AUC of metoprolol were increased by 90% and 229% respectively in the presence of mirabegron (**Tables 2.4.1.2.1 and 2.4.1.2.2).**

Figure 2.4.1.2.1 Mean metoprolol and α-hydroxymetoprolol plasma concentration-Time Profiles in the Absence and Presence of Mirabegron (Study 178-CL-005)

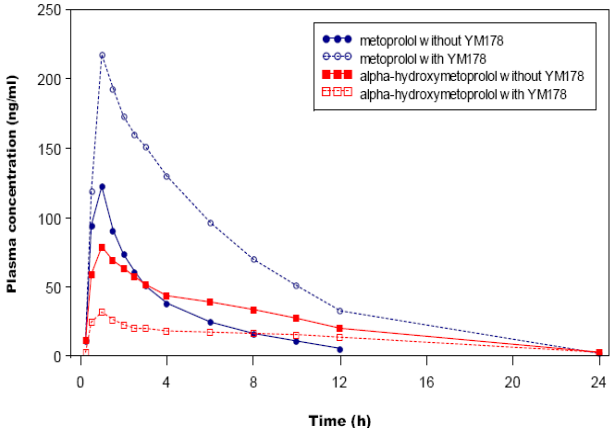


Table 2.4.1.2.1 Summary of PK parameters of metoprolol in the absence and presence of Mirabegron (Study 178-CL-005)

Treatment	Statistic	t_{max}[1] (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	$AUC_{0\text{-}inf}$ (ng.h/ml)	$t_{1/2}$ (h)	CL/F (l/h)	V_z/F (l)
Metoprolol	Mean	0.79	132	408	439	2.96	200	844
	(SD, CV)	(0.26)	(41, 31%)	(147, 36%)	(153, 35%)	(0.35, 12%)	(70, 35%)	(288, 34%)
	Range	0.5 – 1.0	64 – 180	212 – 606	240 – 657	2.3 – 3.5	119 – 325	485 – 1271
	Median	1.0	155	377	402	2.93	195	821
Metoprolol and YM178	Mean	1.25	247	1242	1389	4.11	58.6	346
	(SD, CV)	(0.69)	(67, 27%)	(317, 26%)	(286, 21%)	(0.24, 6%)	(13, 22%)	(72, 21%)
	Range	0.5 – 3.0	133 – 352	821 – 1809	986 – 1845	3.6 – 4.4	42 – 79	250 – 470
	Median	1.0	226	1220	1399	4.17	55.9	321

1. For t_{max} CV was not calculated.

Table 2.4.1.2.2. Statistical Analysis

Analysis Population	Substance	PK parameter	Ratio with/without YM178			Coefficient of variation (%)
			Point estimate	90% Confidence interval		
				Lower	Upper	
PPS	Metoprolol	$AUC_{0\text{-}inf}$	3.285	2.699	3.998	27.3
PPS	Metoprolol	C_{max}	1.897	1.543	2.332	28.7

Reviewer's Comments:

This study confirms the *in vitro* findings that mirabegron is a moderate inhibitor of CYP2D6. The data demonstrates that mirabegron reduces the clearance of metoprolol by inhibition of CYP2D6 and increases its bioavailability by reducing the first-pass effect. Based on the data from this study, metoprolol dose should be adjusted and/or titrated when co-administered with mirabegron.

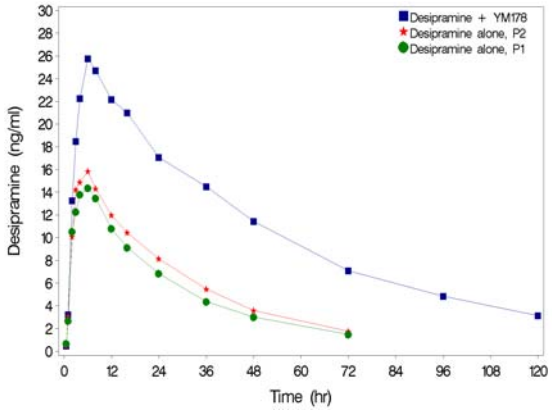
Desipramine (Study 178-CL-058):

This study was a cross-over design with two periods. In period 1, subjects received a single oral dose of 50 mg desipramine on Day 1. From Day 5 up to and including Day 23, subjects received daily oral doses of 100 mg mirabegron. A single dose of

50 mg desipramine was given in combination with mirabegron on Day 18 (13 days after the first dose of mirabegron). In period 2 (after 13 days washout), subjects received a single oral dose of 50 mg desipramine on Day 38.

When coadministerd with mirabegron, there was a marked increase in the plasma concentration-time profiles of desipramine (**Figure 2.4.1.2.2).** The mean Cmax and AUC of desipramine were increased by 79% and 241%, respectively.

Figure 2.4.1.2.2 Mean Plasma Desipramine Concentration-Time Profiles Following Single Dose Administration of 50 mg Desipramine on Days 1, 18 and 38 (Study 178-CL-058)



Reviewer's Comments:

As discussed above in the case of metoprolol, the data for desipramine is additional confirmatory evidence that mirabegron is a CYP2D6 inhibitor. In this case, the dose of desipramine also may need to be adjusted or titrated.

Overall, based on these data from the two studies, caution should be advised when mirabegron is coadministered with metoprolol and desipramine or with CY2D6 substrates, especially those drugs that are known to exhibits a narrow therapeutic index.

It should be noted that in the sponsor's proposed label of the highlight section states the following:

"Caution is advised if mirabegron is co-administered with medication significantly metabolized by CYP2D6 with a narrow therapeutic index (e.g., thioridazine, flecainide, propafenone"

In a tabulated section of the label, the sponsor's recommendation is "caution" for both desipramine and metoprolol.

2.4.1.2.2 Studies with CYP3A4 Substrates:

The potential of mirabegron to inhibit CYP3A *in vivo* was examined with the CYP3A4 substrates ethinyl estradiol (EE) and levonorgestrel (LNG), components of combined oral

contraceptive (COC), and solifenacin a muscarinic receptor antagonist (see earlier Section on the effect of other urologic drugs on mirabegron PK).

Effect of Mirabegron on Oral Contraceptives (Study 178CL-068):

The objective of this study was to determine the effect of multiple doses of 100 mg mirabegron on the PK EE and LNG containing COC.

The study was a double-blind cross-over design. All subjects received a study COC (Minidril®, not US approved) containing 30 mcg EE and 150 mcg LNG. Subjects started their study COC on Day 1 and continued for 21 days in the first study period. After 7 days (without a COC) to allow for break-through bleeding, they re-started the COC for 21 days in the second study period. In each study period, starting on the 12th day of receipt of the COC, subjects received either mirabegron (100 mg once daily) or matching placebo, for 10 days.

The co-administration of mirabegron had no effect on the plasma concentration-time profiles or the PK parameters of EE and LNG on Day 21 (**Figures 2.4.1.2.1).** The ratio of least square means for Cmax and AUC values with and without mirabegron were 0.958 and 0.961, respectively, for EE, and 0.938 and 0.955, respectively, for LNG. The 90% confidence intervals of the treatment ratios were contained entirely within the predefined equivalence limits of 0.80-1.25 (**Table 2.4.1.2.2).**

Figure 2.4.1.2.1 Mean Steady-State Plasma Concentration-Time Profiles for EE and LNG Following Administration of COC Alone or in Combination with Mirabegron 100 mg QD (Study 178-CL-068)

A: EE **B: LNG**

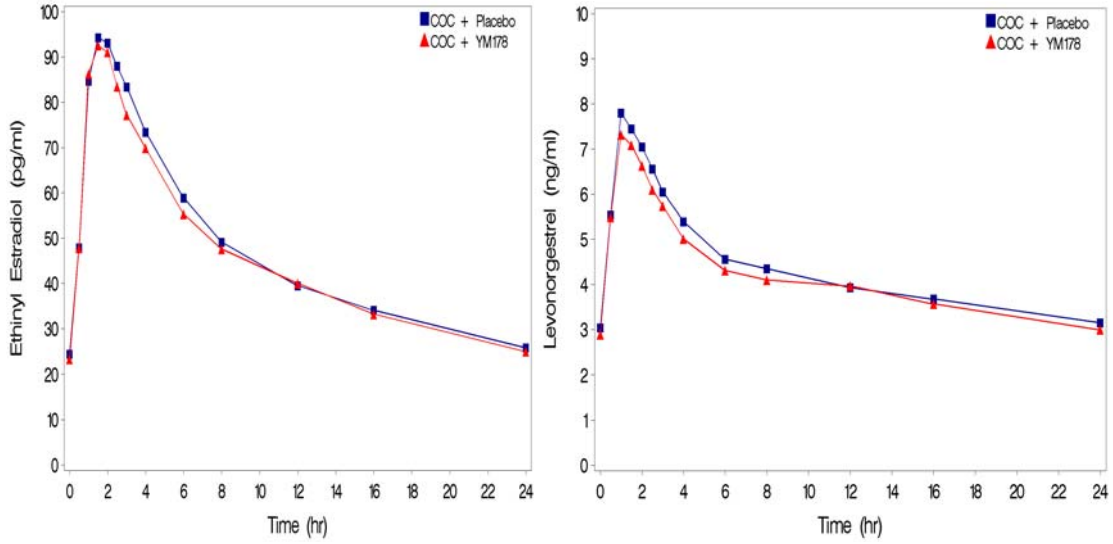


Table 2.4.1.2.2 Statistical Analysis of the Effect of Mirabegron 100 mg Administered QD on PK of EE and LNG on Day 21 (Study 178-CL-068)

Hormone	Parameter	Least Square Means: COC with Placebo (n=23)	Least Square Means: COC with Mirabegron (n=24)	Ratio with/without Mirabegron	90% Confidence Interval
EE	C_{max} (pg/mL)	95.5	91.5	0.958	0.874-1.050
	AUC_{tau} (pg·hr/mL)	1060	1019	0.961	0.886-1.043
LNG	C_{max} (ng/mL)	7.99	7.49	0.938	0.862-1.021
	AUC_{tau} (ng·hr/mL)	98.5	94.0	0.955	0.883-1.032

Reviewer's Comments:

Based on this study mirabegron is not expected to impair hormonal contraceptive efficacy of a combination oral contraceptive containing EE and LNG. However, the data may not be extrapolated to other COC that contains other than EE and LNG. Overall, from this study it can be anticipated that mirabegron may have minimal effect on CYP3A4 substrates.

Effect of Mirabegron on Solifenacin (Study 178CL-069):

This study was described early in Section under the effect of mirabegron on the urologic drugs. Therefore, the study design will not be repeated here. Based on this study the plasma concentration-time profiles of solifenacin and the PK parameters were minimally affected by the co-administration of mirabegron (**Figure 2.4.1.2.2 and Table 2.4.1.2.2**). Solifenacin Cmax and AUC were increased by 23% and 26% as a result of co-administration with mirabegron, respectively.

Figure 2.4.1.2.2 Mean Solifenacin Plasma Concentration-Time Profiles Following Administration of Solifenacin 10 mg Alone (Day 1) or in Combination with Mirabegron 100 mg QD (Day 23) (Study 178-CL-069)

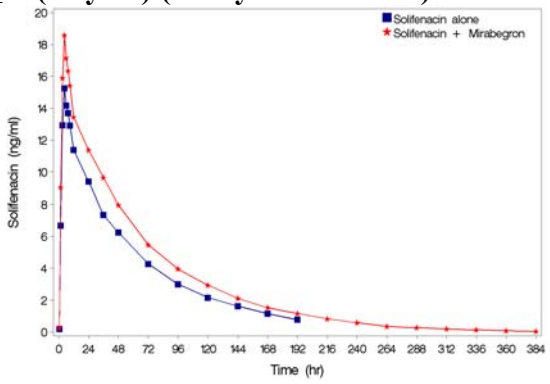


Table 2.4.1.2.2 Statistical Analysis of PK Parameters of Solifenacin Following Administration of Solifenacin 10 mg Alone (Day 1) or in Combination with Mirabegron 100 mg QD (Day 23) (Study 178-CL-069)

Parameter	Least Square Means		Ratio (%) with/without Mirabegron	90% Confidence Interval
	Solifenacin Alone	Solifenacin with Mirabegron		
C_{max} (ng/mL)	15.3	18.8	1.23	1.15, 1.31
AUC_{inf} (ng·hr/mL)	838	1055	1.26	1.17, 1.35

Reviewer's Comments:

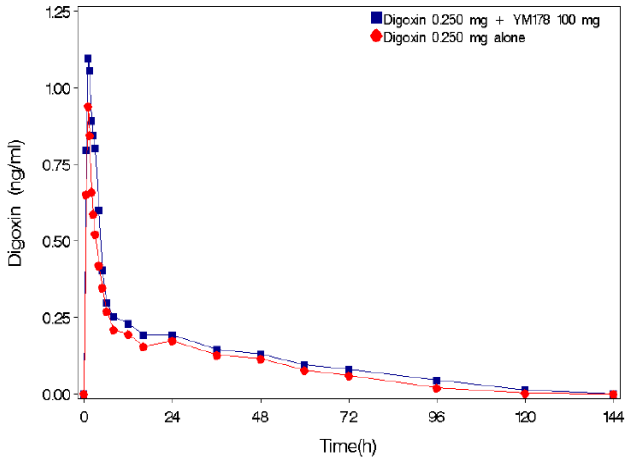
These data further support the observed effect on COC in which mirabegron has minimal effect on CYP3A4. Therefore, mirabegron can be administered with drugs known to be metabolized by CYP3A4.

2.4.1.2.3 Studies with P-gp Substrates:

To investigate the clinical effect of mirabegron on P-gp, the PK of digoxin (single dose of 0.250 mg), was studied with and without coadministration of mirabegron (100 mg qd) [Study 178-CL-059].

The study was crossover at a single oral dose of 0.250 mg digoxin that was administered on Day 1. The PK profile of digoxin was followed up to 144 hours when given alone. On Day 10 up through Day 23, subjects received daily oral doses of 100 mg mirabegon. On Day 18, a single 0.250 mg dose of digoxin was given again in combination with mirabegron (i.e., 8 days after the first dose of mirabegron). The PK profile of digoxin was again followed up to 144 hours. On Day 16 through Day 19, blood samples for mirabegron were collected. There was no change in the plasma concentration-time profiles of digoxin or any of its PK parameters (**Figure 2.4.1.3.1)**

Figure 2.4.1.3.1 Mean Plasma Digoxin Concentration-Time Profiles Following Single Dose Administration of 0.250 mg Digoxin Alone or in Combination with Mirabegron 100 mg Dose (Study 178-CL-059)



Reviewer's Comments:

The results from this study indicate that the inhibitory effect of mirabegron on P-gp is weak. However, as digoxin is a drug with narrow therapeutic index it is recommended that serum digoxin concentrations be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. In addition, it is recommended that the lowest dose for digoxin should initially be used when intended to be co-administered with mirabegron.

2.4.1.2.4 Other Commonly Used Drugs

Interaction with Warfarin (Study 178-CL-040):

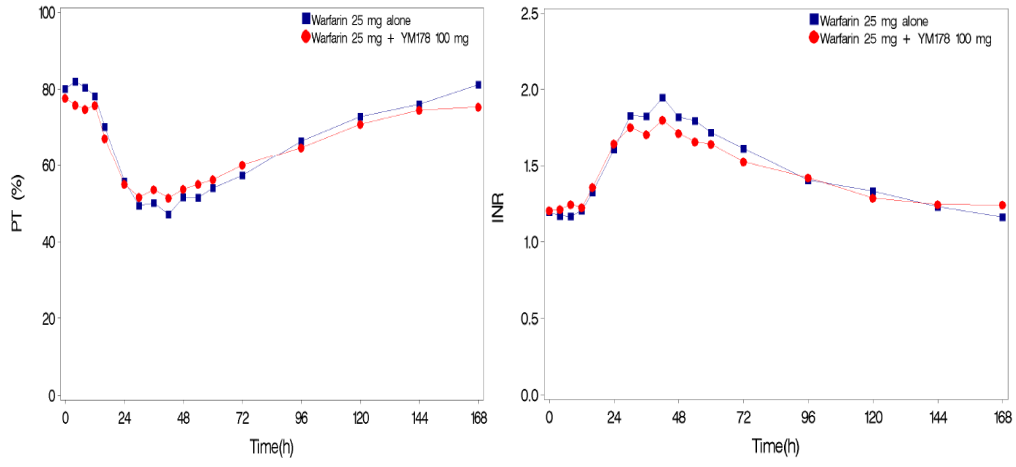
Warfarin is a commonly used drug as anticoagulant and it is known as a CYP2C9 substrate. This study was designed as a crossover following a supratherapeutic single dose of 25 mg of warfarin and in combination with 100 mg mirabegron administered once daily.

On Day 1 and 23 warfarin was administered as a single 25 mg dose followed by a PK sampling post dosing in each day. From Day 15 to Day 30 mirabegron 100 mg daily doses were administered. Thus, warfarin was co-administered with mirabegron only on Day 23.

Mirabegron had no effect on the PK profiles or parameters of S- or R- warfarin. The mean ratios for Cmax were 1.05 and 1.04 (R- and S-warfarin, respectively) and for AUC 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). In addition, mirabegron did not affect the pharmacodynamic (PD) effect of warfarin such as prothrombin time (PT) and international normalized ratio (INR) (**Figure 2.4.2.4.1**).

Figure 2.4.1.2.4.1 Mean Pharmacodynamic (PD) Profiles Following Single Dose Administration of 25 mg Warfarin with and without 100 mg Mirabegron (Study 178-CL-040)

A: PT **B: INR**



Reviewer's Comments:

This study clearly demonstrates that mirabegron had no effect on CYP2C9 substrates as warfarin is well known probe for this isoenzyme. There was no effect on either PK or PD (PT or INR) profiles of warafrin. The supra-therapeutic dose of warfarin used in this study is sufficient to rule out any potential effect of mirabegron on warfarin PD effects. Therefore, warfarin and mirabegron can be concurrently administered without any dose adjustment of either drug.

2.5 General Biopharmaceutics
2.5.1 What is the Effect of Food on the BA of Mirabegron?

The effect of food on the bioavailability of mirabegron was evaluated in 6 Phase 1 studies. The focus of this review is on the pivotal two studies that were conducted in Western (Studies 178-CL-041) and Japanese (178-CL-078) subjects. The other studies are irrelevant as they were conducted using IR tablets. Also, the focus of the review is on the highest recommended dose strength of 50 mg tablet.

Overall, mirabegron OCAS tablets exhibited a decrease in plasma exposure when given with food. However, the extent of absorption is dependent on meal composition and specifically the fat contents (i.e., low-fat versus high-fat). Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron Cmax and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron Cmax and AUC by 75% and 51%, respectively. Similar results were obtained with a 100 mg dose of mirabegron. It should be noted that there was no food restrictions in the primary Phase 3 studies to establish the safety and efficacy of mirabegron.

Study 178-CL-41 was a crossover designed at a dose of 50 mg or 100 mg administered under fasted or fed conditions (high-fat and low-fat breakfasts). The study was conducted in 72 healthy subjects where 18 men and 18 women were enrolled in each arm, 50 mg or 100 mg dose. From this study it can be seen that food in general caused reduction in the bioavailability of mirabegron, the highest effect was noted after taking the drug with low fat food content (**Figures 2.5.1 and 2.5.2 and Tables 2.5.1**). The same trend was also seen for urine excretion data for mirabegron in the same study (**Figure 2.5.2**).

It should also be noted that food had similar effect in the Japanese study, but the mirabegron plasma levels were higher than in Westerners (Compare scale in **Figures, 2.5.3 vs 2.5.1,** 178-CL-078). The study was also conducted after 50 mg and 100 mg OCAS tablets and of similar design as that of the Westerners study (041).

Figure 2.5.1 Mean Plasma Mirabegron Concentration-Time Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions in Western Subjects (Study 178-CL-41)

A: Time scale 0-96 hours **B: Time scale 0-12 hours**

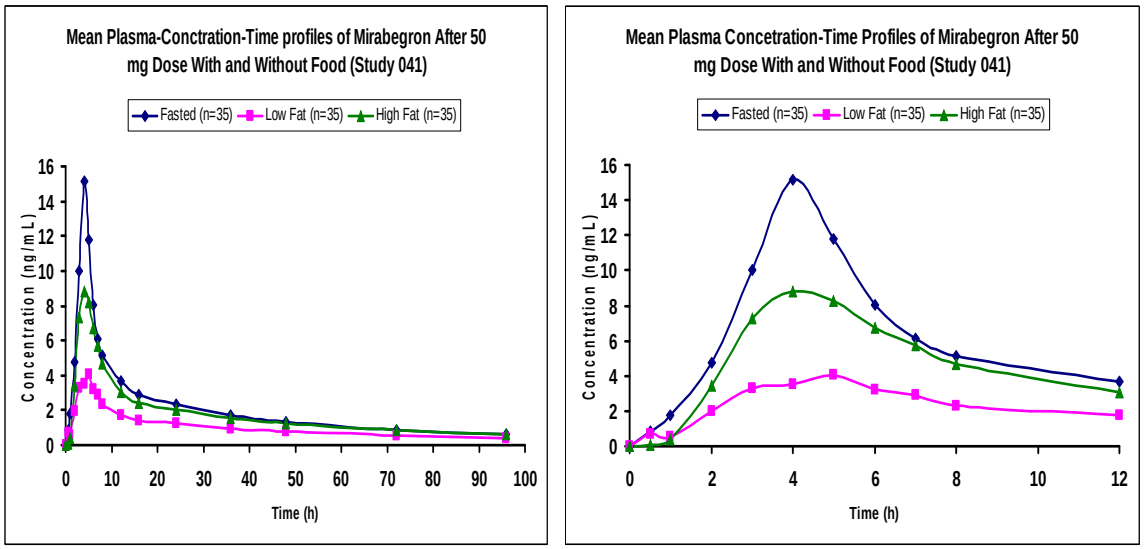


Table 2.5.1 Statistical Analysis of the Effect of Food on Plasma Mirabegron PK Parameters Following Administration of 50 mg Dose under Fasted and Fed Conditions In Western Subjects (Study 178-CL-041)

Parameter (unit)	Treatment	n	LS Mean†	Comparison	LS Mean Ratio (%)‡	90% CI of Ratio (%)‡
AUC_{inf} (hr·ng/mL)	Fasted	35	227.44	Low-fat/Fasted	48.66	(43.32, 54.67)
	Low-fat	36	110.68	High-fat/Fasted	83.24	(74.16, 93.42)
	High-fat	36	189.31	High-fat/Low-fat	171.05	(152.47, 191.89)
AUC_{last} (hr·ng/mL)	Fasted	35	188.42	Low-fat/Fasted	44.29	(38.90, 50.42)
	Low-fat	36	83.45	High-fat/Fasted	80.32	(70.61, 91.36)
	High-fat	36	151.33	High-fat/Low-fat	181.35	(159.52, 206.17)
C_{max} (ng/mL)	Fasted	35	17.75	Low-fat/Fasted	24.96	(19.89, 31.33)
	Low-fat	36	4.43	High-fat/Fasted	54.76	(43.69, 68.65)
	High-fat	36	9.72	High-fat/Low-fat	219.38	(175.08, 274.89)

Figure 2.5.2 Mean (SD) Mirabegron Urinary Cumulative Excretion Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions in Western Subjects (Study 178-CL-41)

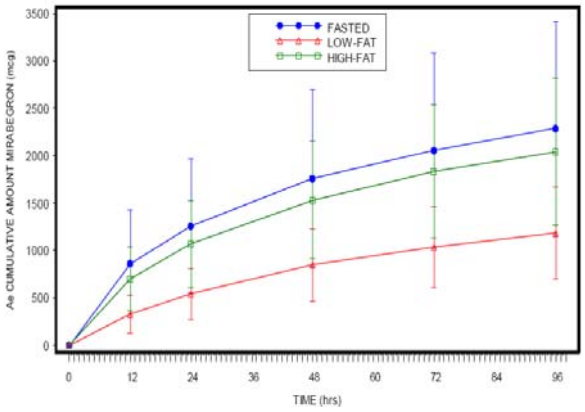
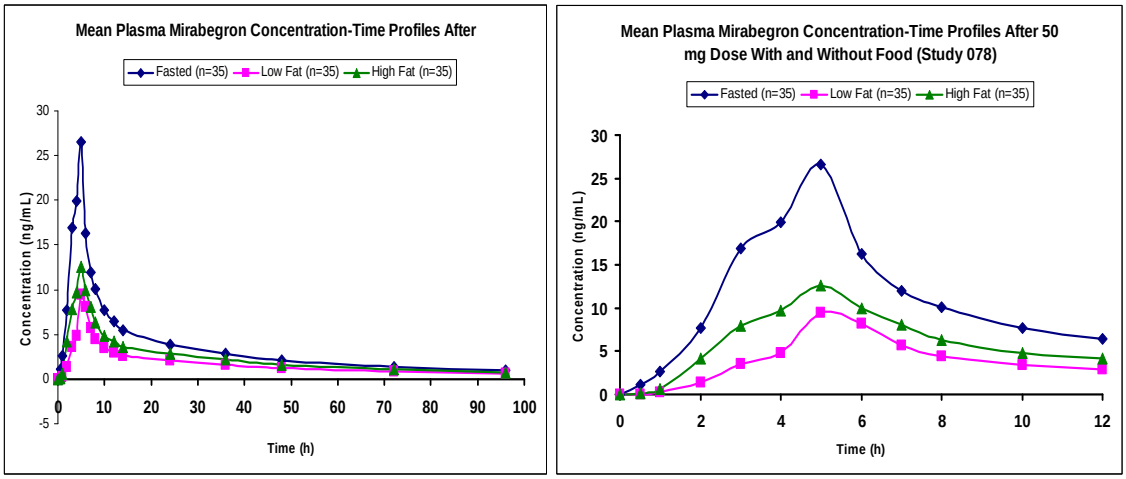


Figure 2.5.3 Mean Plasma Mirabegron Concentration-Time Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions In Japanese Subjects (Study 178-CL-078)

A: Time scale 0-96 hours **B: Time scale 0-12 hours**



Reviewer's Comments:

Food has similar and consistent pattern on the absorption of mirabegron in the above two studies and in all other studies conducted with mirabegron, irrespective of formulation. As stated above, the second pivotal study was in Japanese subjects. **Figures 2.5.4 and 2.5.5** shows the comparison in exposure for mirabegron between Japanese and Westerners following the same 50 mg OCAS dose of mirabegron for the observed and dose and weight normalized (ratio) for Cmax and AUC.

Figure 2.5.4 Comparison of the Effect of Food on Cmax of Miragebron in Westerns (Study 041) and Japanese (Study 078). Data is Expressed as Mean (±SD) of Observed Cmax (Left) and Cmax Normalized by Weight-Adjusted Dose (Right)
A: Observed Cmax B: Cmax normalized by Weight-Adjusted Dose

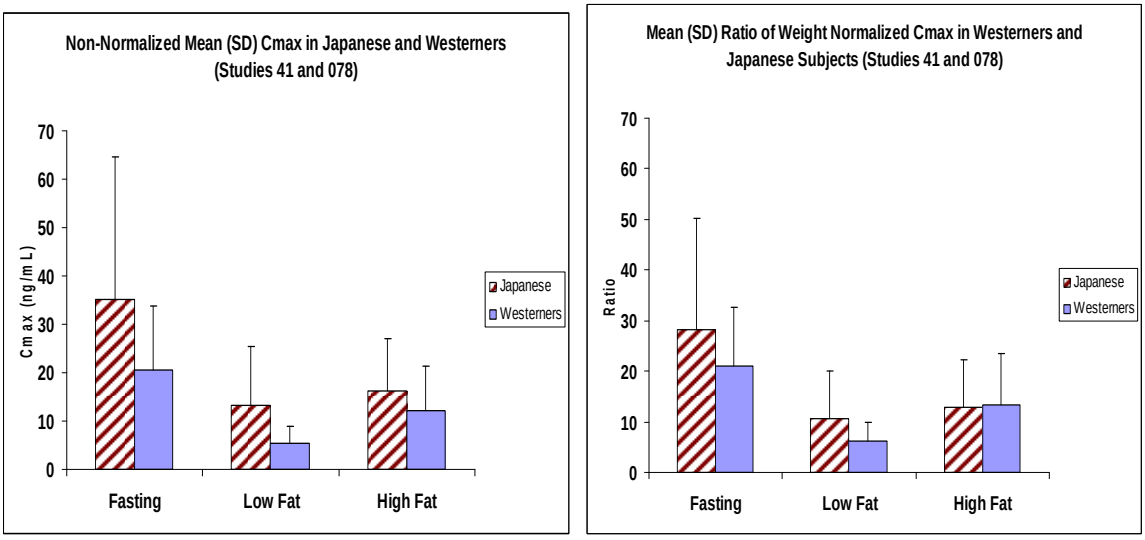
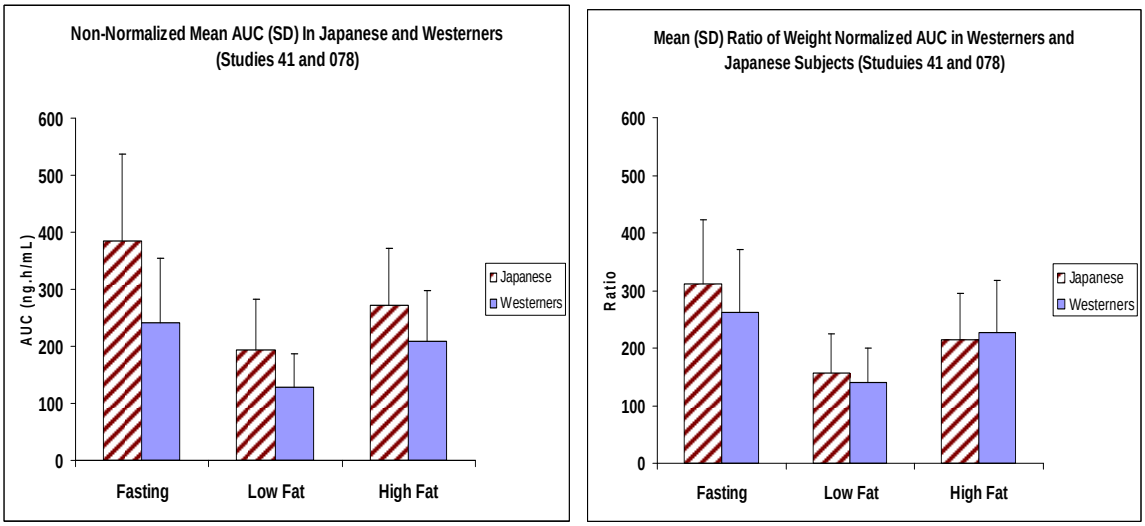


Figure 2.5.5 Comparison of the Effect of Food on AUC of Miragebron in Westerns (Study 041) and Japanese (Study 078). Data is Expressed as Mean (±SD) of Observed AUC (Left) and AUC Normalized by Weight-Adjusted Dose (Right)
A: Observed AUC B: AUC Normalized by Weight-Adjusted Dose



The mean Cmax and AUC were normalized by weight and dose using the observed data from studies 41 and 078 following 50 mg dose in average normal body weight of **70 kg** as follows:

Ratio A (weight-adjusted dose ratio centered at 70 kg) = 70/subject weight
Ratio B (exposure normalized by the weight-adjusted dose) = AUC or Cmax/Ratio A (i.e., weight-adjusted dose ratio centered at 70 kg)

The analysis was performed as two sets. One set for the mean Cmax and AUC and mean body weight in respective study and treatment. The second set was for individual observed Cmax and AUC and individual weights at a respective treatment. It should be noted that the mean body weight in Japanese study was 57.92 Kg ranging from 46.2-74.0 K and in Westerners study the mean body weight was 77.31 Kg ranging from 55.2 to 103.6 kg.

By normalizing the mean Cmax for mean body weight adjusted dose in each study the difference between Japanese and Westerners subjects became minimal for the mean and individual Cmax and AUC data, especially after food. Based on this analysis, it appears that the observed difference in exposure between Japanese and Westerners can be explained by weight difference between the two populations. It should be noted that based on the pharmacogenomic review no genetic factors were found to be associated with the PK and/or the metabolism of mirabegron.

To conclude, in all studies the data is conclusive that food reduces the absorption of mirabegron. Also it was consistently observed that low fat content appears to lower the bioavailability of mirabegron at greater extent than high fat content. Overall, the exposure of mirabegron is consistently higher in Japanese compared to Westerners following the same dose. It should be noted that the pivotal Phase 3 studies were conducted irrespective food or food contents and the sponsor proposed label states that mirabegron is to be taken with or without food.

2.5.2 Was the to-be-Marketed Formulation Used in the Clinical Trials?

Various dosage forms and formulations of mirabegron have been used through different stages of clinical development.

The early clinical studies were conducted with immediate release (IR) capsules and tablets. An aqueous solution was used for the human mass balance study. Since the IR formulations showed a considerable decrease in plasma exposure with food and high peak-to-trough fluctuations in plasma concentrations with once daily dosing, a modified release tablet using Oral Control Absorption System (OCAS) technology was developed. OCAS modified release formulation is also referred to as extended-release or prolonged-release. Several OCAS formulations, with differing dissolution profiles were screened in one study (Study 178-CL-030).

Based on the data from 178-CL-30 study, an OCAS tablet with an intermediate dissolution rate (OCAS-M) was selected for further development. The release rate of mirabegron from this OCAS formulation resulted in a PK profile with a slower rate of absorption than the IR tablet, an attenuated food effect with a high-fat meal and reduced fluctuations in plasma concentrations compared with once daily mirabegron IR.

The OCAS tablet was used in the phase 2 and 3 efficacy studies and all clinical pharmacology studies, with the exception of those investigating the effect of cytochrome

P450 (CYP) 2D6 genotype and DDIs with metoprolol (Study 178-CL-005) and metformin (Study 178-CL-006), and the mass balance study (Study 178-CL-007).

The sponsor made minimal changes to the OCAS tablet formulation during clinical development. There were minor differences in the formula and granulating method between OCAS tablets used in the initial phase 1 studies and those used during the phase 2b stage of clinical development. *In vitro* release of mirabegron was not influenced by these changes (see ONDQA review). It is important to note that 50-mg tablets used in phase 2b and Phase 3 were identical in terms of composition and manufacturing process.

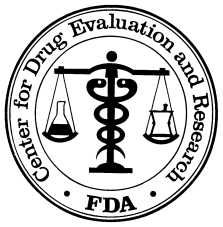
For 25 mg and 100 mg strengths, used in Phase 2b and Phase 3 were differed only in film-coating agents used to improve the visual identification for the final products. Dissolution profiles demonstrated that these formulations exhibited similar release characteristics *in vitro* (See ONDQA review).

2.5.3 Is there Dosage Strength Equivalency?

The sponsor did not conduct dosage-strength equivalency study between 2 x 25 mg tablets and 1 x 50 mg tablet. However, to establish similarity between the two tablet strengths the sponsor conducted *in vitro* dissolution data and performed *in-vitro-in-vivo*-correlation (IVIVC) analysis. According to ONDQA review, the dissolution profiles for both strengths were similar and the similarity factor (f2) was >50 for all tested batches of both strengths.

Reviewer's Comments:

Based on this data and the overall safety and efficacy profiles of mirabegron and the data from QTc study at a high dose there is no need to conduct a separate study to specifically evaluate the dosage-strength equivalency between 2 x 25 mg and 1 x 50 mg tablets. Therefore, the *in vitro* data alone in this case is acceptable (see also ONDQA review). It should be noted that 25 mg tablet is reserved for patients with renal and hepatic impairment, depending on the severity.



Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

REVIEW OF ELEVATED BLOOD PRESSURE LEVELS

C

DEVELOPMENT INDICATION: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

CONSULT QUESTIONS: With respect to the sponsor's interpretations of the vital signs data from phase III studies in their Cardiovascular Research Report (NDA-CTD module 5.3.5.3),

1. Does the DCRP consultant agree with sponsor's assessment of the effect of mirabegron on blood pressure?
2. Does the DCRP consultant agree with sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been found to be associated with an increased cardiovascular risk?
3. Are there any differences in mirabegron's effects on blood pressure in the pre-hypertensive, hypertensive 1, 2 or 3 groups?
4. Please refer to Table 22 page 70 and Figure 15 page 93 of report. Please provide your assessment of the sponsor's categorical analysis based upon proportions of blood pressure outliers?

DOCUMENTS AVAILABLE FOR REVIEW:
NDA 202611 submissions, with particular attention to CTD Module 5.3.5.3, entitled Cardiovascular Research Report (CRR), the Integrated Summary of Safety (ISS), Individual Phase III FSRs, and analysis datasets.

Summary Assessment and Recommendation

DCRP agrees with the sponsor's assessment of the effect of mirabegron on blood pressure. There is no evidence that pre-existing hypertension (Hypertension Status 1 definition) increases the risk of medically important elevations in SBP or DBP in patients treated with mirabegron relative to the normotensive population.

Categorical changes from baseline displayed in Table 22 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. This may be an artifact of the program design, in that all of the phase III tolterodine data in this table is 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 $\leq$ 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.

We do not agree with the sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been

found to be associated with an increased cardiovascular risk. Increasing risks for cardiovascular events with increasing levels of blood pressure are a continuum (i.e., these risk curves 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 much 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.

We recommend that the sponsor put the target population's characteristics into a Framingham risk model so that they can predict what the likely impact will be on CV event rates for the observed blood pressure effects. This can be done using the actual data for each subject's true blood pressure shifts (as opposed to assuming that all patients experienced the mean change in BP seen for the overall/integrated clinical trial data). If the target population's baseline Framingham risk for CV events is low, then the effect of small BP elevations will be small, but non-zero. For the patients who are at substantially higher Framingham risk (i.e. the high-BMI, diabetic, hypertensive smokers over the age of 70), the effect of these same small BP increments may be more impressive, and a benefit/risk determination different for a higher baseline risk subgroup. This analysis should be performed both for mirabegron and for the tolterodine positive control that was incorporated into the phase III program.

Introduction

Overactive Bladder (OAB)

OAB is a syndrome that includes urgency as an essential symptom, associated with increased urinary frequency and urge urinary incontinence. Its etiology is not completely understood, but overactivity of the detrusor muscle, an indicator of increased bladder sensitivity to contraction-mediating neurotransmitters and mediators originating from the urothelium have been observed. Detrusor overactivation involves afferent signaling and conveys a bladder sensation of urgency in OAB patients. Currently, antimuscarinic agents are used as a standard therapy for overactive bladder; however, their mechanism of action can be associated with inhibition of bladder contractile force during urination which can lead to impaired voiding function. Antimuscarinics have also been associated with adverse events such as dry mouth, constipation, and blurred vision.

During filling, the human urinary bladder is under control of the sympathetic nerve system and the release of noradrenalin leads to activation of both alpha 1 and beta-ARs in the bladder. During filling, the relaxation-mediating beta-ARs functionally dominate the contraction-mediating alpha 1-ARs in the bladder leading to detrusor muscle relaxation. Functional pharmacology studies as well as mRNA expression data have shown that the beta 3-AR is the dominant beta-AR involved in relaxation of the human urinary bladder.

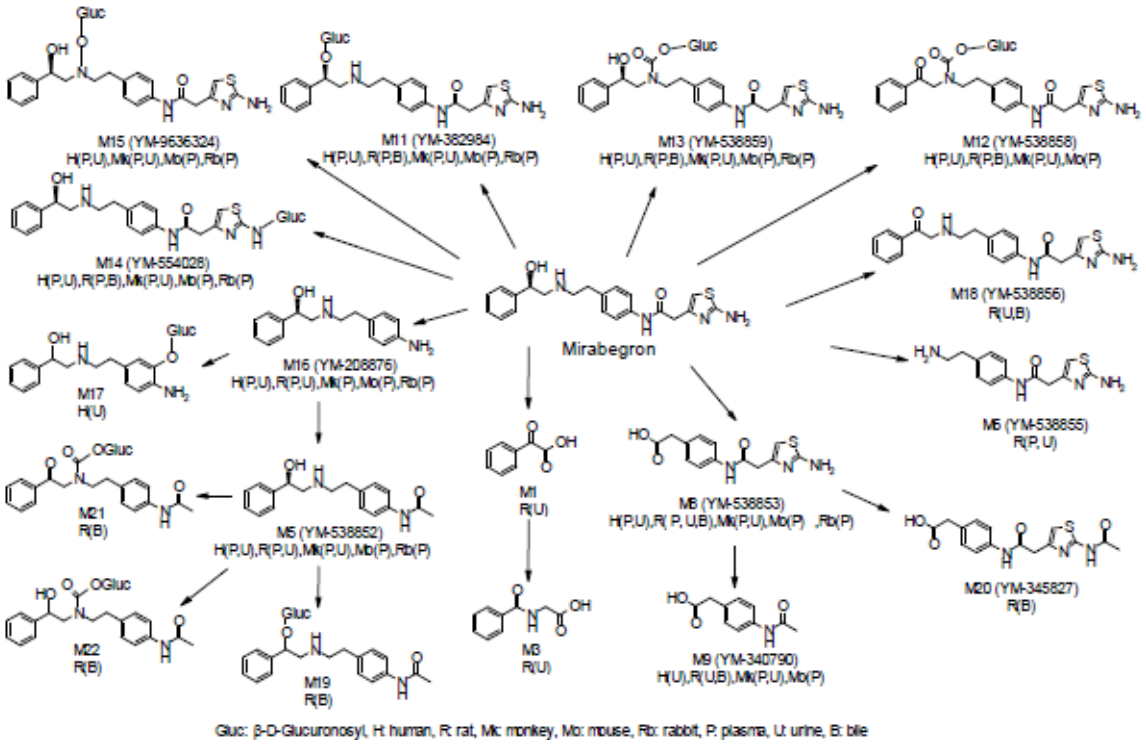
The beta-AR family consists of beta 1, beta 2 and beta 3-ARs. The distribution and function of the various beta-AR subtypes differ in the detrusor muscles from different

species. The beta 3-AR is the functionally dominant beta-AR for bladder relaxation in man, cynomolgus monkey, dog and rat, whereas, in cats and guinea pigs, beta 1-ARs are functionally dominant in the bladder. On the other hand in rabbit bladder, beta 2- subtype is dominant [Nergardh et al, 1977; Yamazaki et al, 1998; Takeda, Yamazaki, Akahane et al, 2002].

Mirabegron

Mirabegron is a relatively selective small molecule agonist of the beta 3-AR with a fairly complex in vivo metabolism as shown in
Figure 1 below (from figure 1 of the sponsor's nonclinical overview):

Figure 1. Postulated Metabolic Pathways of Mirabegron



According to the sponsor, the two major metabolites, M11 and M12, are devoid of relevant pharmacological activity.

In humans, the elimination pathway of radioactivity was higher through urinary than for fecal excretion, with the urinary excretion comprising 55.0% and fecal excretion 34.2% of the total radioactivity administered after oral administration of a single 160 mg dose of ^{14}Cmirabegron. In vitro studies and chemical structures of the metabolites suggest that butyrylcholinesterase, uridine diphospho-glucuronosyltransferase (UGT), cytochrome P450 (CYP) 3A4 and 2D6 enzymes, and possibly alcohol dehydrogenase are involved in the metabolism of mirabegron.

Oral controlled absorption system (OCAS) mirabegron reaches Cmax between 3.0 and 4.3 hours after both single and multiple dosing. Bioavailability increases with dose due to saturation of efflux transporters in the intestine. Steady state concentrations are achieved within 7 days of once daily dosing. Steady state concentrations after once daily administration are approximately double that of single dose administration. Mirabegron is extensively distributed. The effective half-life is approximately 19 hours and the terminal elimination half-life is approximately 50 hours.

In the receptor binding study using membrane fractions from Chinese hamster ovary (CHO) cells expressing human beta-AR subtypes, mirabegron showed high affinity for the human beta 3-AR (105-fold higher affinity for beta 3-AR versus beta 1-AR and 33-fold higher affinity for beta 3-AR vs beta 2-AR), as seen in **Table 1** below (from sponsor's non-clinical overview):

Table 1. Affinity of Mirabegron for Human Beta-AR Subtypes

	Ki (nmol/L)		
Test article	**Beta 1**	**Beta 2**	**Beta 3**
Mirabegron	4,200 ± 900	1,300 ± 300	40 ± 20.2

Ki values are expressed as the mean ± SE of 3 runs.

Agonistic activity of mirabegron to beta-AR subtypes (beta 1-, 2-, and 3-AR) from human was examined with CHO cells expressing each of these beta AR subtypes. Intracellular cyclic adenosine monophosphate (cAMP) concentrations were used as an indicator of beta-AR agonistic activity. Mirabegron showed an agonistic activity to the human beta 3-AR with a 50% effective concentration (EC_{50}) value of 1.5 nmol/L [Module 2.6.2, Section 2.1.2.1, Study 178-PH-044]. The intrinsic activity at the human beta 3-AR, defined as the cAMP concentration relative to the maximum response induced by isoproterenol, for mirabegron was 0.8, indicating that mirabegron is a full agonist at this receptor subtype. On the other hand, mirabegron showed intrinsic activities for human beta 1- and beta 2-AR of 0.1, and 0.2, respectively, and the potency was low as compared to that at the human beta 3-AR [Module 2.6.2, Section 2.1.2.1, Study 178-PH-044].

Regulatory and Clinical Development Background

Mirabegron, a beta-3 AR, is a first in mechanistic class, new molecular entity (NME) being submitted under NDA 202611 for the treatment of overactive bladder. Mirabegron was approved in 2011 in Japan for the treatment of OAB, and the Japanese label was submitted as part of NDA 202611.

In Phase 1 studies of mirabegron, several patients reported mild increases in blood pressure. Therefore, the review division voiced a concern about increases in heart rate possibly coupled with increases in blood pressure. The sponsor agreed to conduct intensive assessment of vital signs in phase 2 and phase 3 studies. The mirabegron NDA

application is being submitted simultaneously with the MAA application to the European Medicines Agency for the Centralized Procedure. The US and EU applications share a common efficacy and safety data package.

The sponsor notes that evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from 3 randomized, placebo-controlled studies (046, 047, and 074) conducted in North America and Europe. The protocols for primary phase 3 studies 046 and 047 were submitted for SPA review in December 2007.

As part of phase 3 evaluation, patients measured their own home blood pressures. Blood pressure and pulse rate were measured at Visit 1 (screening) by the investigator, using the device that the patient was going to use for self-measurement thereafter. The investigator measured the circumference of the upper arm to give the patient the right cuff type. The blood pressure measurement was performed in the sitting position at both arms. The arm with the highest blood pressure was taken for the following blood pressure measurements, which were to be done by the patient during the 5 diary days preceding Visits 2, 3, 4, 5 and 6 (baseline, and Weeks 1, 4, 8 and 12) after waking up in the morning and between 2 and 4 p.m. At Visit 1, the investigator instructed the patient on how to perform and document in the diary the self-measurement of the blood pressure and pulse rate according to the "Guidelines for measuring blood pressure at home" (Current Medical Research and Opinion 2002, 18(4): 177-184, CHMP Guidelines, CPMP/EWP/238/95 Rev.2 Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, European Medicines Agency, London, 23 June 2004). Three readings were taken, each about 2 minutes apart. The patient kept records of the readings (date, time, pulse rate, systolic and diastolic pressure were documented). The sponsor makes the following summary statements/conclusions from their analyses of these data:

- The adjusted mean differences vs placebo for change from baseline in systolic blood pressure (SBP) in the EU/NA OAB 12-week Phase 3 study population for mirabegron 25, 50 and 100 mg and tolterodine were -0.5, 0.6, 0.4 and -0.1 mm Hg for AM measurements and -1.0, 0.5, 0.9 and -0.0 mm Hg for PM measurements, respectively. The adjusted mean differences vs placebo for change from baseline diastolic BP (DBP) in the EU/NA OAB 12-week Phase 3 study population for mirabegron 25, 50 and 100 mg and tolterodine were -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.

- In the EU/NA Long-term Controlled Study 178-CL-049, the adjusted mean changes from baseline SBP/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 and -0.3, 0.1 and -0.0 mm Hg for PM measurements. 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 and -0.0, 0.1 and 0.6 mm Hg for PM measurements.

- 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 similar across all treatment groups.

- The observed increases in SBP/DBP appeared to be reversible upon discontinuation of treatment.

- In both the EU/NA OAB 12-week Phase 3 and EU/NA Long-term Controlled Study populations, the proportions of patients meeting categorical criteria for decreases in SBP and DBP (e.g. ≥ 15 and ≥ 20 mmHg) were low and similar across the mirabegron, placebo and tolterodine treatment groups.

- The Sponsor states that small incremental increases in vital signs such as 1 mm Hg elevation in blood pressure have not been found to be associated with an increased cardiovascular risk.

With respect to the consult questions, the review division calls DCRP's attention to CTD Module 5.3.5.3, entitled Cardiovascular Research Report (CRR), noting that that ambulatory BP monitoring (ABPM) was not performed during the mirabegron drug development program, nor was it requested by the review division.

In the sponsor's CRR, evaluations for cardiovascular safety parameters were focused on the following 3 populations:

- **Global OAB 12-week Phase 2/3**: This population consists of pooled data from 6 placebo-controlled double-blind 12-week phase 2/3 studies conducted globally in Europe, North America, Japan and Australia in 7514 patients with OAB (Studies 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074). Three of the 6 studies also included tolterodine extended release (ER) 4 mg as an active comparator group.

- **EU/NA OAB 12-week Phase 3**: This population is a subset of the Global OAB 12-week Phase 2/3 Population and includes pooled data from 3 placebo-controlled, double-blind, 12-week phase 3 studies conducted in Europe, North America and Australia/New Zealand (henceforth described as Europe and North America) in 4611 patients with OAB (Studies 178-CL-046, 178-CL-047 and 178-CL-074). One of the 3 studies also included tolterodine ER 4 mg as an active comparator group.

- **EU/NA Long-term Controlled**: This population consists of Study 178-CL-049, a 12-month, double-blind phase 3 study with an active-controlled tolterodine ER 4 mg comparator arm conducted in Europe, North America, Australia/New Zealand and South Africa (henceforth described as Europe and North America) in 2444 patients with OAB. Patients who had previously participated in studies 046 and 047 could enroll in this study if they met the inclusion/exclusion criteria.

In the 12 week studies, changes from baseline of cuff blood pressure measurements (triplicate measures for 5 days preceding clinic visit) were analyzed with descriptive statistics, average change from baseline using an ANCOVA model with treatment group, geographical region, and sex as fixed factors and baseline value as a covariate, and repeated measure methodology (the model for which contains terms for treatment group, baseline measurement, time (each relevant visit), time by treatment group, gender, gender by time, and geographical region). In the Long-term Controlled study, changes from baseline of cuff blood pressure measurements were also analyzed using both ANCOVA and repeated measures models. In a small ABPM sub-study within study 049, mean SBP/DBP values were calculated for each patient based on the non-missing measurements taken every 15 minutes over 24 hours prior to baseline, at month 6, and at month 12, and these data analyzed with a repeated measures model (ANCOVA analysis was not performed for the ABPM parameters). Except for the ABPM analyses, missing data was handled using LOCF methodology.

Assessments and Answers to Questions

1. **Do you agree with sponsor's assessment of the effect of mirabegron on blood pressure? Specifically, is the Sponsor's summary of the results of blood pressure monitoring (summary statements in bullet points above) accurate?**

   Assuming that no data integrity issues were found during the primary medical review, and that the data integration was done correctly, the sponsor's summary from the CRR describes accurately the overall central tendency and categorical data results obtained for the integrated EU/NA OAB 12 week studies, as well as the EU/NA long-term study (see tables 10, 11, 18, 19, 22, and 23 of the CRR). For convenience of review, the CRR is linked to this document in DARRTS, and is embedded here for ease of reference to these tables:

   
   CRR.pdf

   Interestingly, for the BP data, it appears that patients that were not on beta blockers had smaller changes than those on beta blockers, though the changes in both groups were small.

   Additional evidence for the minimal overall effects of mirabegron on SBP, DBP, and Pulse based on the phase III clinical trial data is demonstrated by the sponsor in study ISN 178-PK-016, titled, "*Modeling to explore the relationship between mirabegron exposure and selected cardiovascular safety parameters (i.e. pulse rate, diastolic and systolic blood pressures) in overactive bladder patients*." In this study, the hemodynamic effects of mirabegron were assessed from an integrated dataset including one phase II study that tested the 50 mg dose (study 044), and the two pivotal phase III trials that were given SPA approval by the review division (studies

046 and 047). Study 074, a third phase III trial that tested a lower range of doses, but included the 50 mg dose, was used for external validation of the generated models for predicting HR and BP responses to various exposures of mirabegron. The integrated results for dose-specific and exposure-specific effects of mirabegron on individual changes from baseline for Pulse, DBP, and SBP, are shown below in Figures 5, 14, and 23 as excerpted from the study ISN 178-PK-016 FSR:

Figure 5: Individual morning and afternoon pulse rate change from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose (bottom graph). The dashed black lines are smoothes through the data. The plain black zero lines indicate no change from baseline.

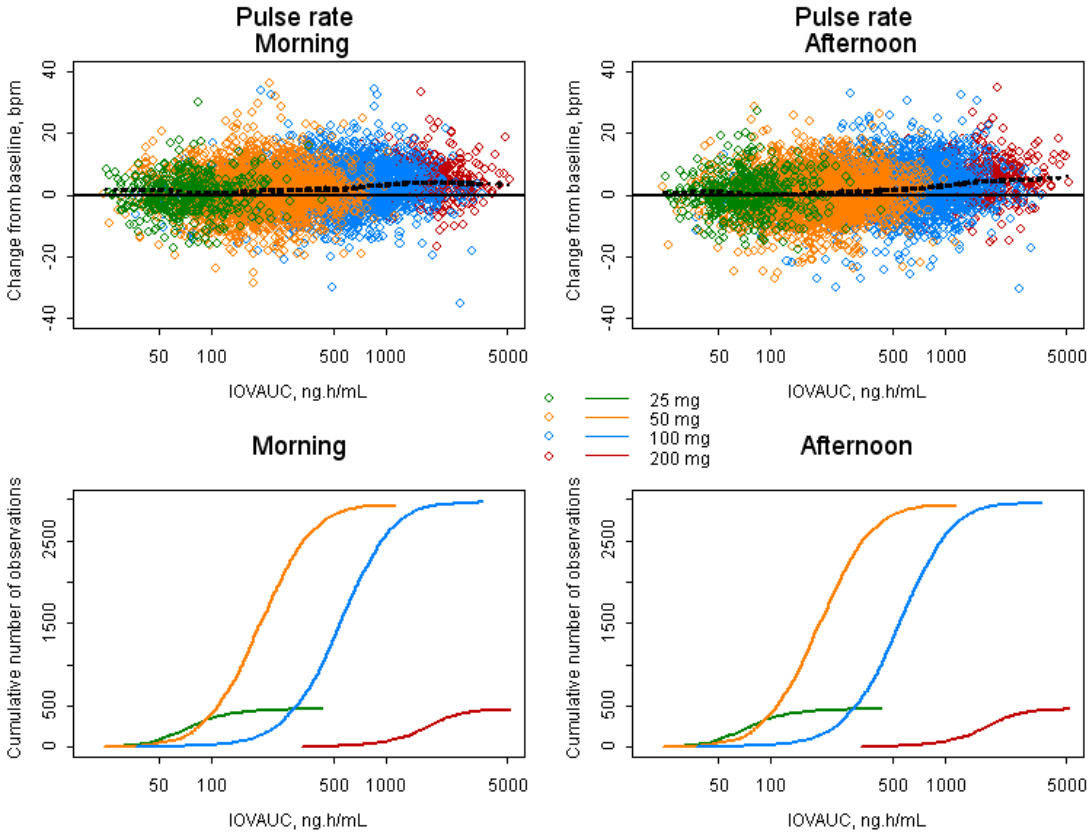


Figure 14: Individual morning and afternoon diastolic blood pressure (DBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose (bottom graphs). The dashed black lines are smoothes through the data. The solid black lines indicate no change from baseline.

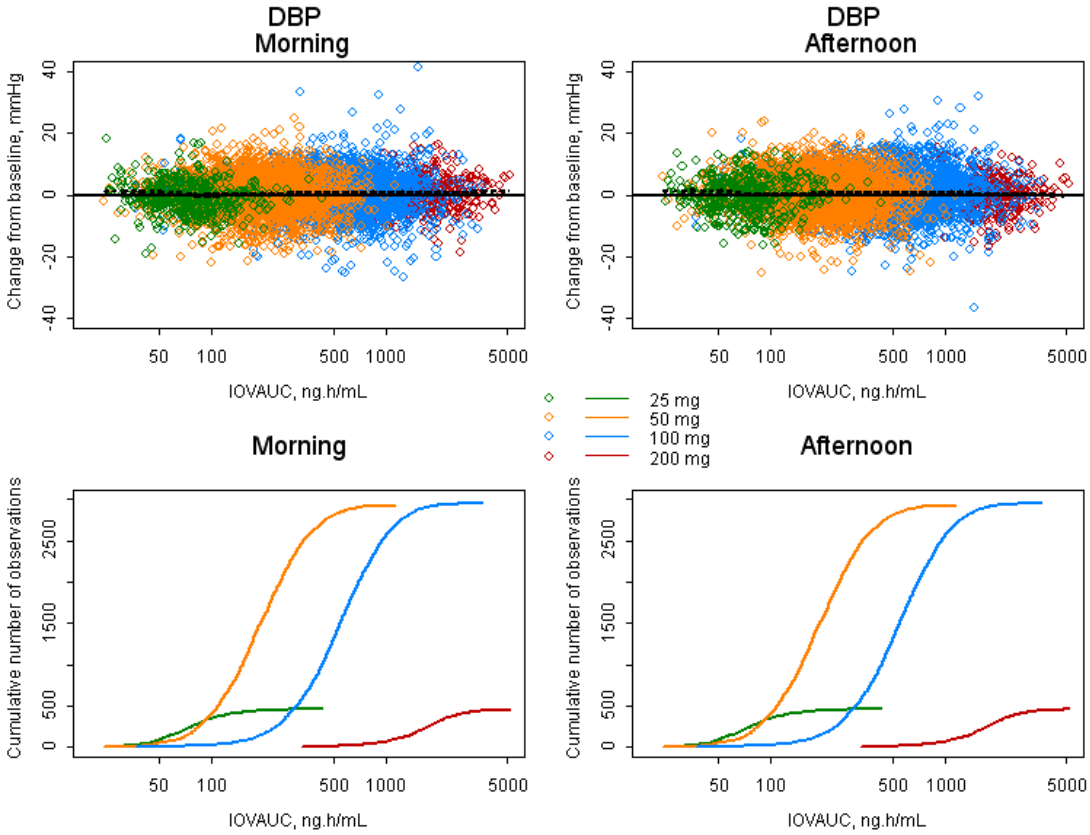
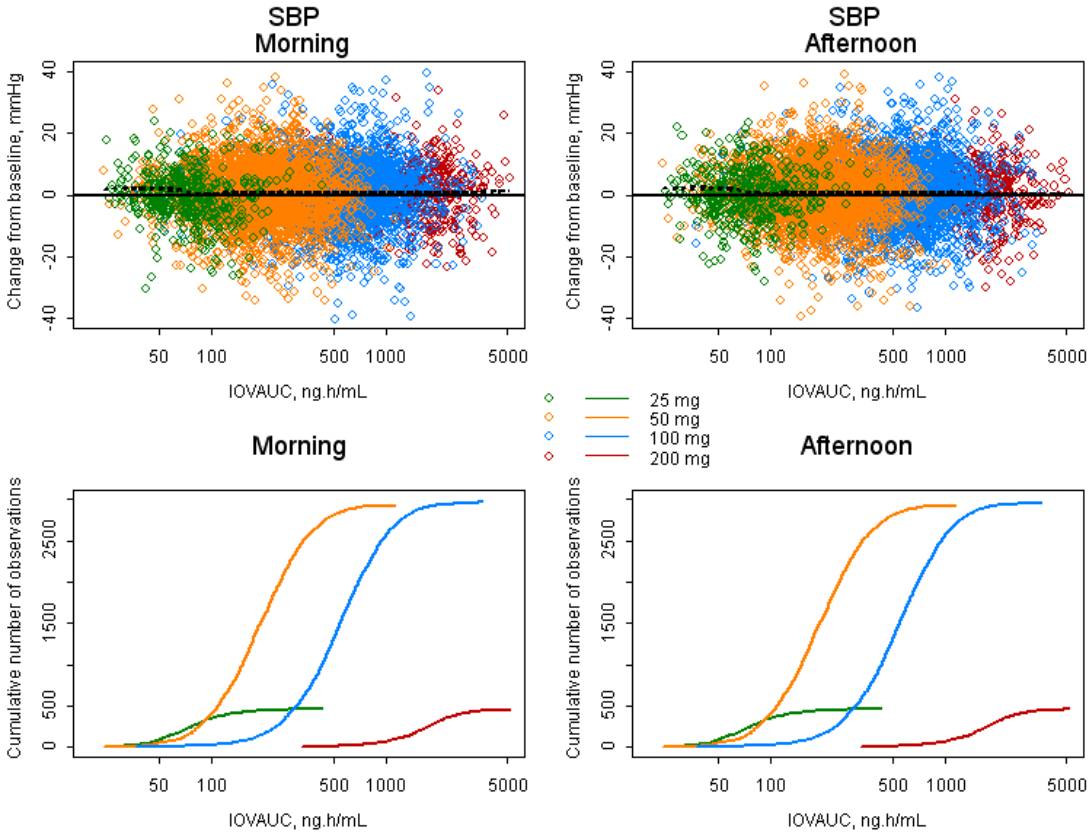


Figure 23. Individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose level (bottom graph). The dashed black lines are smoothes through the data. The solid black zero lines indicate no change from baseline.



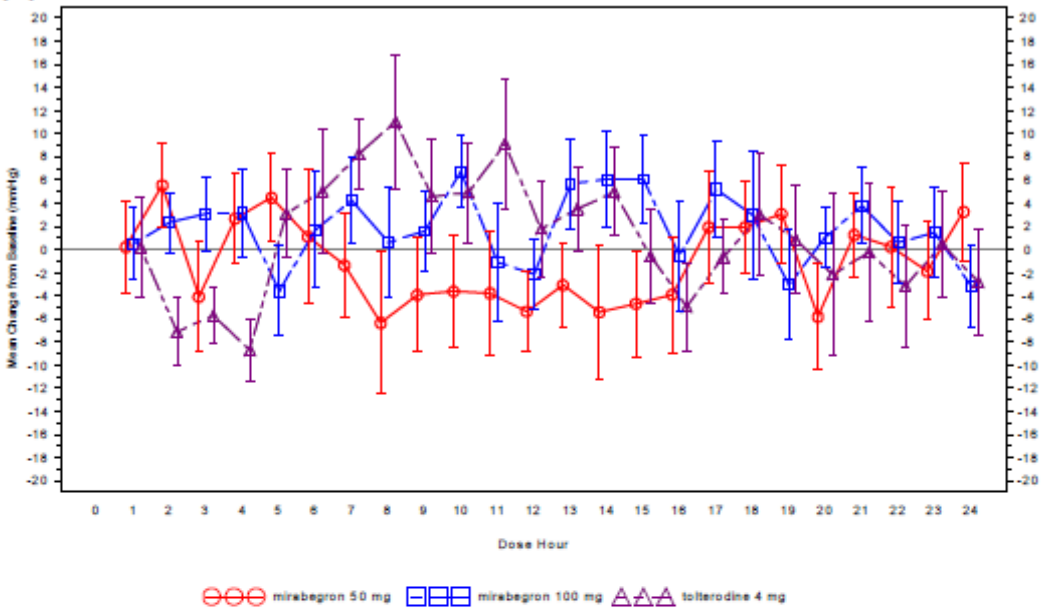
Finally, data supporting the limited impact of 50mg mirabegron on SBP and DBP comes from the small ABPM sub-study in the EU/NA Long-term Controlled Population that was performed in a subset of patients at selected investigational sites in the US (n = 21 for mirabegron 50 mg; n = 28 for mirabegron 100 mg; and n = 24 for tolterodine); pulse rate and blood pressure assessments were collected for a 24-hour period prior to visits at baseline, month 6 and month 12. The ABPM data for SBP and DBP is excerpted below for each post-baseline visit in Table 43 and for month 12 in Figure 29 from the sponsor's CRR. Overall, mirabegron demonstrated SBP/DBP effects similar to those of tolterodine, and a dose response in SBP/DBP effects between 50 mg and 100 mg mirabegron was demonstrated.

Table 43 **Summary of Mean Change from Baseline to Month 6, Month 12 and Final Visit in ABPM Mean 24-hour SBP and DBP Measurements, EU/NA Long-term Controlled Population**

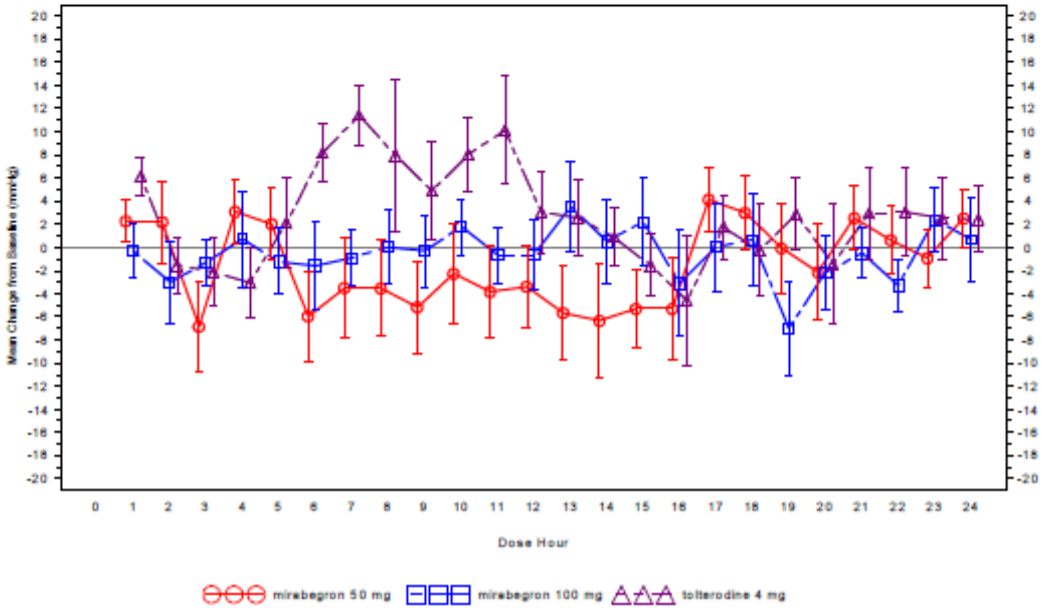
Parameter (mm Hg)	Mirabegron				Tolterodine ER 4 mg	
	50 mg		100 mg			
	SBP	DBP	SBP	DBP	SBP	DBP
	(n = 21)		(n = 28)		(n = 24)	
Baseline						
Mean (SD)	124.0 (15.30)	72.9 (6.07)	122.7 (12.30)	72.6 (7.27)	125.9 (13.25)	71.8 (8.25)
Median	119.2	73.9	120.4	71.2	127.0	69.6
Range	105 to 171	62 to 87	106 to 155	59 to 87	97 to 149	59 to 91
Month 6						
n	15	15	16	16	13	13
Mean (SD)	119.4 (13.43)	70.5 (4.79)	120.5 (12.40)	72.4 (10.26)	122.6 (8.00)	71.7 (7.58)
Median	118.2	69.0	119.8	70.2	119.0	73.7
Range	100 to 157	65 to 82	101 to 152	60 to 96	112 to 134	54 to 82
Change from baseline to month 6						
Mean (SD)	-3.2 (7.51)	-2.6 (5.20)	1.9 (7.05)	-0.1 (4.13)	-0.5 (7.62)	0.9 (6.24)
Median	-4.5	-4.4	2.4	0.1	-3.9	0.3
Range	-13 to 10	-11 to 5	-13 to 15	-8 to 9	-11 to 15	-10 to 14
Month 12						
n	10	10	12	12	9	9
Mean (SD)	120.6 (13.71)	70.4 (5.52)	120.8 (11.44)	72.7 (8.85)	121.8 (11.70)	71.6 (6.59)
Median	118.4	70.2	117.0	71.3	122.4	71.8
Range	104 to 155	65 to 82	107 to 146	60 to 89	102 to 142	63 to 83
Change from baseline to month 12						
Mean (SD)	-1.3 (8.76)	-1.7 (5.24)	1.5 (7.24)	-0.7 (5.25)	1.1 (5.78)	2.7 (4.06)
Median	2.0	-0.9	-1.0	-1.3	0.3	2.8
Range	-16 to 10	-11 to 5	-7 to 20	-6 to 14	-10 to 11	-3 to 8
Final visit						
n	15	15	16	16	13	13
Mean (SD)	119.5 (11.84)	70.0 (4.76)	119.5 (10.39)	71.3 (8.37)	122.4 (10.38)	72.2 (7.40)
Median	117.1	69.9	117.0	69.7	122.4	72.7
Range	104 to 155	65 to 82	107 to 146	60 to 89	102 to 142	59 to 83
Change from baseline to final visit						
Mean (SD)	-3.0 (7.71)	-3.0 (4.85)	0.9 (7.16)	-1.3 (4.75)	-0.7 (5.83)	1.4 (5.22)
Median	-3.4	-4.5	-1.0	-2.2	-0.6	2.5
Range	-16 to 10	-11 to 5	-9 to 20	-6 to 14	-10 to 11	-10 to 8

Figure 28 **Mean Change from Time-matched Baseline in Blood Pressure at Month 12 Measured by ABPM, EU/NA Long-term Controlled Population**

(A) SBP



(B) DBP



Note that the global OAB population was not assessed for vital sign changes, according to the sponsor, due to lack of concordance of data structures (i.e., vital signs not systematically recorded in a way that could be integrated from the other studies). I would prefer that they submit some sort of summary analysis of this data, rough though it undoubtedly is, just to see what's in it.

2. **Do you agree with sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been found to be associated with an increased cardiovascular risk?**

   No, we do not agree. Increasing risks for cardiovascular events with increasing levels of blood pressure are a continuum (i.e., these risk curves 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. Therefore, the absolute risk of increasing SBP from 169 to 170 is much 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.

   We recommend that the sponsor put the target population's characteristics into a Framingham risk model so that they can predict what the likely impact will be on CV event rates for the observed blood pressure effects. This can be done using the actual data for each subject's true blood pressure shifts (as opposed to assuming that all patients experienced the mean change in BP seen for the overall/integrated clinical trial). If the target population's baseline Framingham risk for CV events is low, then the effect of small BP elevations will be small, but non-zero. For the patients who are at substantially higher Framingham risk (i.e. the high-BMI, diabetic, hypertensive smokers over the age of 70), the effect of these same small BP increments may be more impressive, and a benefit/risk determination different for a higher baseline risk subgroup.

   This analysis should be performed both for mirabegron and for the tolterodine positive control that was incorporated into the phase III program.

3. **Are there any differences in mirabegron's effects on blood pressure in the pre-hypertensive, hypertensive 1, 2 or 3 groups?**

   There were two definitions of hypertension that were assessed in the sponsor's CRR as follows:

   - Hypertension Status 1 (clinical history)
     - Hypertensive – any patient with a medical history of hypertension and receiving concurrent antihypertensive treatment at the time of the screening visit
     - Past History of Hypertension: any patient with a medical history of hypertension and no concurrent antihypertensive treatment at the time of the screening visit. Patients included in the past history of hypertension were also included in the normotensive population.
     - Normotensive: any patient who did not meet the definition of hypertensive

   - Hypertension Status 2 (JNC-7 definitions)
     - Normal: SBP < 120 mm Hg AND DBP < 80 mm Hg

- Prehypertension: SBP 120 to 139 mm Hg OR DBP 80 to 89 mm Hg
- Stage 1 Hypertension: SBP 140 to 159 mm Hg OR DBP 90 to 99 mm Hg
- Stage 2 Hypertension: SBP ≥ 160 mm Hg OR DBP ≥ 100 mm Hg

Hypertension Status 1 definitions were primarily utilized in the clinical development program, so all of the in-text displays of the CRR are based on these criteria. Accordingly, all of the following data displays in this section are based on the Hypertension Status 1 definitions. Hypertension Status 2 definitions were utilized only to generate a series of tables in the CRR that included descriptive statistics for SBP, DBP, and change in these parameters at protocol-specified follow-up intervals. Manual review of this sequence of Hypertension Status 2 descriptive statistics in the CRR reveals no medically important differences in the change from baseline SBP/DBP parameters between the 50mg mirabegron and tolterodine groups. Further analysis based on Hypertension Status 2 nomenclature would be of limited utility, since the categorical analyses already performed by the sponsor are defined by absolute shifts in SBP/DBP. It is possible (and in fact not surprising) that the JNC7 stage 2 patients may be the ones that are demonstrating the more prominent BP shifts in the categorical analysis tables, but this would undoubtedly be the case across all treatment groups.

From CRR Appendix 4 (Comprehensive Summary of Blood Pressure), Tables 3, 4, 5, 6, 10, and 11 corroborate the mirabegron's minimal and comparator-similar impact on change from baseline of SBP and DBP in the short-term and long-term phase III studies:

Table 3 **Change from Baseline to Final Visit in SBP Measured by Patient Diary, ANCOVA Model, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1**

Population Parameter (mm Hg)	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
AM					
Normotensive†	**(n = 857)**	**(n = 250)**	**(n = 873)**	**(n = 555)**	**(n = 300)**
n	825	239	845	532	289
Baseline mean (SE)	121.4 (0.55)	123.8 (0.97)	121.9 (0.55)	120.2 (0.63)	123.8 (0.85)
Adjusted mean change from baseline (SE)	0.6 (0.29)	0.2 (0.62)	1.4 (0.28)	1.2 (0.37)	-0.0 (0.52)
Mean difference vs placebo (SE)		-0.4 (0.67)	0.7 (0.40)	0.6 (0.48)	-0.7 (0.61)
95% 2-sided CI		-1.7, 0.9	-0.1, 1.5	-0.3, 1.5	-1.9, 0.5
Past history of hypertension†	**(n = 58)**	**(n = 22)**	**(n = 67)**	**(n = 35)**	**(n = 15)**
n	54	20	65	33	15
Baseline mean (SE)	136.9 (1.97)	134.7 (3.64)	137.7 (2.19)	131.8 (3.07)	132.5 (2.66)
Adjusted mean change from baseline (SE)	-0.3 (1.36)	-0.1 (2.56)	-2.0 (1.27)	-3.9 (1.88)	-1.7 (2.85)
Mean difference vs placebo (SE)		0.3 (2.86)	-1.6 (1.85)	-3.5 (2.36)	-1.3 (3.20)
95% 2-sided CI		-5.4, 5.9	-5.3, 2.0	-8.2, 1.1	-7.7, 5.0
Hypertensive†	**(n = 523)**	**(n = 182)**	**(n = 502)**	**(n = 374)**	**(n = 195)**
n	504	171	482	359	187
Baseline mean (SE)	133.4 (0.74)	136.8 (1.16)	134.2 (0.76)	132.3 (0.87)	134.8 (1.22)
Adjusted mean change from baseline (SE)	-0.5 (0.45)	-1.2 (0.92)	0.1 (0.46)	-0.5 (0.57)	0.2 (0.81)
Mean difference vs placebo (SE)		-0.7 (1.01)	0.6 (0.65)	0.0 (0.73)	0.7 (0.94)
95% 2-sided CI		-2.7, 1.3	-0.7, 1.9	-1.4, 1.4	-1.1, 2.6
PM					
Normotensive†	**(n = 857)**	**(n = 250)**	**(n = 873)**	**(n = 555)**	**(n = 300)**
n	824	239	845	532	289
Baseline mean (SE)	122.1 (0.50)	125.5 (0.89)	122.9 (0.51)	120.8 (0.59)	125.4 (0.78)
Adjusted mean change from baseline (SE)	0.9 (0.29)	0.0 (0.63)	1.4 (0.29)	2.2 (0.38)	0.5 (0.54)
Mean difference vs placebo (SE)		-0.8 (0.69)	0.5 (0.41)	1.3 (0.49)	-0.4 (0.62)
95% 2-sided CI		-2.2, 0.5	-0.3, 1.3	0.3, 2.2	-1.6, 0.8
Past history of hypertension†	**(n = 58)**	**(n = 22)**	**(n = 67)**	**(n = 35)**	**(n = 15)**
n	54	20	65	33	15
Baseline mean (SE)	133.3 (1.59)	131.2 (3.02)	136.9 (1.94)	130.6 (2.34)	134.3 (2.83)
Adjusted mean change from baseline (SE)	-0.5 (1.41)	-0.3 (2.65)	-2.2 (1.32)	-1.6 (1.94)	3.6 (2.94)
Mean difference vs placebo (SE)		0.1 (2.95)	-1.7 (1.93)	-1.1 (2.43)	4.1 (3.30)
95% 2-sided CI		-5.7, 6.0	-5.5, 2.1	-5.9, 3.7	-2.4, 10.6

Table continued on next page

Hypertensive†	**(n = 523)**	**(n = 182)**	**(n = 502)**	**(n = 374)**	**(n = 195)**
n	502	171	482	358	187
Baseline mean (SE)	129.9 (0.65)	133.9 (1.08)	130.3 (0.70)	127.9 (0.78)	130.5 (1.08)
Adjusted mean change from baseline (SE)	0.1 (0.46)	-1.2 (0.92)	0.6 (0.47)	0.2 (0.58)	0.4 (0.82)
Mean difference vs placebo (SE)		-1.3 (1.02)	0.5 (0.65)	0.1 (0.74)	0.3 (0.95)
95% 2-sided CI		-3.3, 0.7	-0.8, 1.8	-1.3, 1.6	-1.6, 2.2

Table 4 **Change from Baseline to Final Visit in SBP Measured by Patient Diary, ANCOVA Model, EU/NA Long-term Controlled Population, Hypertension status 1**

Population Parameter (mm Hg)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
AM			
Normotensive†	**(n = 488)**	**(n = 509)**	**(n = 478)**
n	474	498	469
Baseline mean (SE)	122.3 (0.70)	121.9 (0.67)	122.1 (0.67)
Adjusted mean change from baseline (SE)	0.3 (0.38)	1.0 (0.37)	-0.3 (0.38)
95% 2-sided CI	-0.4, 1.1	0.3, 1.7	-1.1, 0.4
Past history of hypertension†	**(n = 33)**	**(n = 52)**	**(n = 43)**
n	31	51	43
Baseline mean (SE)	133.1 (2.88)	134.5 (2.34)	129.9 (2.49)
Adjusted mean change from baseline (SE)	-2.8 (1.67)	-0.5 (1.31)	-2.9 (1.41)
95% 2-sided CI	(-6.1, 0.5)	(-3.1, 2.1)	(-5.7, -0.1)
Hypertensive†	**(n = 324)**	**(n = 311)**	**(n = 334)**
n	317	304	324
Baseline mean (SE)	133.4 (0.87)	132.6 (0.88)	133.7 (0.80)
Adjusted mean change from baseline (SE)	0.0 (0.59)	-0.4 (0.60)	-0.7 (0.58)
95% 2-sided CI	-1.1, 1.2	-1.6, 0.7	-1.9, 0.4
PM			
Normotensive†	**(n = 488)**	**(n = 509)**	**(n = 478)**
n	474	498	469
Baseline mean (SE)	123.5 (0.62)	123.3 (0.61)	123.4 (0.62)
Adjusted mean change from baseline (SE)	-0.4 (0.39)	0.9 (0.38)	-0.0 (0.39)
95% 2-sided CI	-1.1, 0.4	0.2, 1.6	-0.8, 0.7
Past history of hypertension†	**(n = 33)**	**(n = 52)**	**(n = 43)**
n	31	51	43
Baseline mean (SE)	131.6 (2.58)	133.6 (1.95)	130.9 (2.06)
Adjusted mean change from baseline (SE)	-1.8 (1.78)	1.1 (1.40)	-4.4 (1.49)
95% 2-sided CI	(-5.4, 1.7)	(-1.6, 3.9)	(-7.3, -1.4)
Hypertensive†	**(n = 324)**	**(n = 311)**	**(n = 334)**
n	315	304	324
Baseline mean (SE)	130.8 (0.79)	129.6 (0.80)	130.6 (0.75)
Adjusted mean change from baseline (SE)	-0.2 (0.58)	-1.0 (0.59)	-0.1 (0.57)
95% 2-sided CI	-1.4, 0.9	-2.2, 0.1	-1.2, 1.1

Table 5 **Change from Baseline to Final Visit in DBP Measured by Patient Diary, ANCOVA Model, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1**

Population Parameter (mm Hg)	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
AM					
Normotensive†	**(n = 857)**	**(n = 250)**	**(n = 873)**	**(n = 555)**	**(n = 300)**
n	825	239	845	532	289
Baseline mean (SE)	76.1 (0.31)	76.4 (0.58)	76.2 (0.30)	76.1 (0.38)	75.4 (0.48)
Adjusted mean change from baseline (SE)	0.4 (0.20)	0.2 (0.42)	0.7 (0.19)	0.7 (0.26)	1.0 (0.36)
Mean difference vs placebo (SE)		-0.2 (0.46)	0.3 (0.28)	0.4 (0.33)	0.6 (0.42)
95% 2-sided CI		-1.1, 0.7	-0.2, 0.9	-0.3, 1.0	-0.2, 1.4
Past history of hypertension†	**(n = 58)**	**(n = 22)**	**(n = 67)**	**(n = 35)**	**(n = 15)**
n	54	20	65	33	15
Baseline mean (SE)	82.7 (1.33)	76.9 (2.43)	84.5 (1.07)	81.0 (2.03)	81.6 (2.14)
Adjusted mean change from baseline (SE)	0.0 (0.89)	-0.8 (1.68)	-1.0 (0.82)	1.6 (1.22)	-0.4 (1.85)
Mean difference vs placebo (SE)		-0.8 (1.87)	-1.0 (1.21)	1.6 (1.53)	-0.4 (2.08)
95% 2-sided CI		-4.5, 2.9	-3.4, 1.4	-1.4, 4.6	-4.5, 3.7
Hypertensive†	**(n = 523)**	**(n = 182)**	**(n = 502)**	**(n = 374)**	**(n = 195)**
n	504	171	482	358	187
Baseline mean (SE)	78.9 (0.43)	80.8 (0.76)	78.8 (0.41)	79.4 (0.45)	79.0 (0.65)
Adjusted mean change from baseline (SE)	-0.5 (0.27)	-0.6 (0.54)	-0.1 (0.27)	-0.6 (0.34)	0.4 (0.48)
Mean difference vs placebo (SE)		-0.0 (0.60)	0.4 (0.38)	-0.1 (0.43)	1.0 (0.55)
95% 2-sided CI		-1.2, 1.1	-0.3, 1.2	-1.0, 0.7	-0.1, 2.0
PM					
Normotensive†	**(n = 857)**	**(n = 250)**	**(n = 873)**	**(n = 555)**	**(n = 300)**
n	824	239	845	532	289
Baseline mean (SE)	75.2 (0.29)	75.5 (0.57)	75.4 (0.31)	75.1 (0.36)	75.2 (0.46)
Adjusted mean change from baseline (SE)	0.6 (0.20)	0.2 (0.43)	0.9 (0.20)	1.4 (0.26)	1.7 (0.36)
Mean difference vs placebo (SE)		-0.4 (0.46)	0.3 (0.28)	0.8 (0.33)	1.1 (0.42)
95% 2-sided CI		-1.3, 0.5	-0.2, 0.9	0.2, 1.5	0.3, 2.0
Past history of hypertension†	**(n = 58)**	**(n = 22)**	**(n = 67)**	**(n = 35)**	**(n = 15)**
n	54	20	65	33	15
Baseline mean (SE)	79.6 (1.21)	74.8 (2.71)	83.0 (1.29)	80.2 (1.87)	80.9 (2.48)
Adjusted mean change from baseline (SE)	-0.7 (0.95)	-3.2 (1.79)	-0.8 (0.88)	1.3 (1.30)	3.0 (1.98)
Mean difference vs placebo (SE)		-2.5 (1.98)	-0.1 (1.29)	1.9 (1.63)	3.7 (2.22)
95% 2-sided CI		-6.5, 1.4	-2.7, 2.4	-1.3, 5.1	-0.7, 8.1
Hypertensive†	**(n = 523)**	**(n = 182)**	**(n = 502)**	**(n = 374)**	**(n = 195)**
n	502	171	482	358	187
Baseline mean (SE)	75.5 (0.40)	76.8 (0.75)	75.5 (0.40)	75.6 (0.44)	75.6 (0.66)
Adjusted mean change from baseline (SE)	0.0 (0.28)	-0.2 (0.57)	0.5 (0.29)	0.1 (0.36)	1.0 (0.50)
Mean difference vs placebo (SE)		-0.2 (0.63)	0.4 (0.40)	0.1 (0.45)	1.0 (0.58)
95% 2-sided CI		-1.4, 1.1	-0.3, 1.2	-0.8, 0.9	-0.2, 2.1

Table 6 **Change from Baseline to Final Visit in DBP Measured by Patient Diary, ANCOVA Model, EU/NA Long-term Controlled Population, Hypertension status 1**

Population Parameter (mm Hg)	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
AM			
Normotensive†	**(n = 488)**	**(n = 509)**	**(n = 478)**
n	474	498	469
Baseline mean (SE)	76.4 (0.38)	76.1 (0.36)	76.5 (0.39)
Adjusted mean change from baseline (SE)	-0.2 (0.25)	0.8 (0.25)	0.2 (0.26)
95% 2-sided CI	-0.7, 0.3	0.3, 1.3	-0.3, 0.7
Past history of hypertension†	**(n = 33)**	**(n = 52)**	**(n = 43)**
n	31	51	43
Baseline mean (SE)	84.5 (1.56)	78.6 (1.21)	80.4 (1.67)
Adjusted mean change from baseline (SE)	-1.3 (1.14)	-0.7 (0.88)	-0.2 (0.94)
95% 2-sided CI	-3.6, 1.0	-2.5, 1.0	-2.1, 1.6
Hypertensive†	**(n = 324)**	**(n = 311)**	**(n = 334)**
n	317	304	324
Baseline mean (SE)	79.4 (0.52)	79.0 (0.49)	79.0 (0.47)
Adjusted mean change from baseline (SE)	-0.4 (0.35)	-0.3 (0.35)	-0.0 (0.34)
95% 2-sided CI	-1.1, 0.2	-1.0, 0.4	-0.7, 0.6
PM			
Normotensive†	**(n = 488)**	**(n = 509)**	**(n = 478)**
n	474	498	469
Baseline mean (SE)	76.1 (0.36)	75.9 (0.36)	76.1 (0.38)
Adjusted mean change from baseline (SE)	0.1 (0.26)	0.4 (0.26)	0.4 (0.27)
95% 2-sided CI	-0.4, 0.6	-0.1, 0.9	-0.1, 1.0
Past history of hypertension†	**(n = 33)**	**(n = 52)**	**(n = 43)**
n	31	51	43
Baseline mean (SE)	82.0 (1.22)	77.1 (1.14)	80.3 (1.36)
Adjusted mean change from baseline (SE)	-0.6 (1.14)	-0.4 (0.89)	-1.7 (0.95)
95% 2-sided CI	-2.9, 1.7	-2.1, 1.4	-3.6, 0.2
Hypertensive†	**(n = 324)**	**(n = 311)**	**(n = 334)**
n	315	304	324
Baseline mean (SE)	76.4 (0.53)	76.0 (0.50)	76.1 (0.46)
Adjusted mean change from baseline (SE)	-0.2 (0.36)	-0.3 (0.37)	0.9 (0.36)
95% 2-sided CI	-0.9, 0.5	-1.0, 0.4	0.2, 1.6

Table 10 **Adjusted Mean Difference vs Placebo for Change (SE) from Baseline to Each Visit in SBP, by Hypertension Status 1, EU/NA OAB 12-week Phase 2/3 Population**

Parameter (mm Hg)	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Normotensive										
Baseline	825	824	239	239	845	845	532	532	289	289
n	121.4	122.1	123.8	125.5	121.9	122.9	120.2	120.8	123.8	125.4
Mean (SE)	(0.55)	(0.50)	(0.97)	(0.89)	(0.55)	(0.51)	(0.63)	(0.59)	(0.85)	(0.78)
Week 4										
n	825	824	239	239	841	841	531	531	288	288
Adjusted mean change from baseline (SE)	0.0 (0.26)	0.4 (0.27)	-0.4 (0.55)	-0.4 (0.56)	0.7 (0.26)	0.8 (0.27)	1.0 (0.34)	1.4 (0.35)	-0.7 (0.47)	-0.0 (0.48)
Mean difference vs placebo (SE)			-0.4 (0.60)	-0.8 (0.62)	0.7 (0.37)	0.4 (0.38)	1.0 (0.43)	1.0 (0.44)	-0.8 (0.55)	-0.4 (0.56)
95% 2-sided CI			(-1.6, 0.8)	(-2.0, 0.4)	(-0.0, 1.4)	(-0.3, 1.2)	(0.2, 1.9)	(0.1, 1.8)	(-1.8, 0.3)	(-1.5, 0.7)
Week 8										
n	767	767	231	231	795	795	500	500	280	280
Adjusted mean change from baseline (SE)	0.3 (0.28)	0.5 (0.29)	-0.0 (0.57)	0.1 (0.59)	1.3 (0.28)	1.3 (0.29)	1.5 (0.36)	1.9 (0.37)	-1.1 (0.50)	-0.1 (0.51)
Mean difference vs placebo (SE)			-0.3 (0.63)	-0.4 (0.65)	1.0 (0.39)	0.8 (0.41)	1.2 (0.46)	1.5 (0.47)	-1.4 (0.58)	-0.6 (0.59)
95% 2-sided CI			(-1.5, 0.9)	(-1.7, 0.9)	(0.2, 1.8)	(0.0, 1.6)	(0.3, 2.1)	(0.5, 2.4)	(-2.5, -0.3)	(-1.8, 0.6)
Week 12										
n	749	749	224	224	769	769	489	489	267	267
Adjusted mean change from baseline (SE)	0.7 (0.30)	1.0 (0.30)	0.3 (0.60)	-0.1 (0.61)	1.5 (0.29)	1.5 (0.30)	1.2 (0.38)	2.3 (0.39)	-0.1 (0.52)	0.5 (0.53)
Mean difference vs placebo (SE)			-0.5 (0.66)	-1.1 (0.68)	0.8 (0.42)	0.5 (0.43)	0.5 (0.48)	1.2 (0.49)	-0.9 (0.61)	-0.5 (0.62)
95% 2-sided CI			(-1.8, 0.8)	(-2.4, 0.3)	(-0.1, 1.6)	(-0.3, 1.3)	(-0.4, 1.5)	(0.3, 2.2)	(-2.1, 0.3)	(-1.7, 0.7)
Past history of hypertension										
Baseline	54	54	20	20	65	65	33	33	15	15
n	136.9	133.3	134.7	131.2	137.7	136.9	131.8	130.6	132.5	134.3
Mean (SE)	(1.97)	(1.59)	(3.64)	(3.02)	(2.19)	(1.94)	(3.07)	(2.34)	(2.66)	(2.83)
Week 4										
n	54	54	20	20	64	64	33	33	15	15
Adjusted mean change from baseline (SE)	-0.6 (1.34)	-1.7 (1.28)	-0.8 (2.42)	-0.4 (2.33)	-1.6 (1.25)	-0.5 (1.20)	-0.6 (1.80)	1.7 (1.73)	-3.7 (2.71)	1.9 (2.60)
Mean difference vs placebo (SE)			-0.2 (2.73)	1.3 (2.62)	-1.1 (1.82)	1.2 (1.75)	-0.0 (2.27)	3.4 (2.18)	-3.1 (3.06)	3.6 (2.93)
95% 2-sided CI			(-5.6, 5.2)	(-3.8, 6.5)	(-4.7, 2.5)	(-2.2, 4.7)	(-4.5, 4.5)	(-0.9, 7.7)	(-9.2, 2.9)	(-2.2, 9.4)
Week 8										
n	51	51	19	19	64	64	30	30	15	15
Adjusted mean change from baseline (SE)	-0.3 (1.29)	-1.5 (1.33)	3.1 (2.34)	-1.2 (2.41)	-2.0 (1.18)	-0.7 (1.23)	-1.2 (1.77)	1.6 (1.82)	-3.2 (2.58)	0.8 (2.66)
Mean difference vs placebo (SE)			3.4 (2.63)	0.3 (2.72)	-1.7 (1.74)	0.8 (1.81)	-0.9 (2.21)	3.2 (2.27)	-2.9 (2.91)	2.3 (2.99)
95% 2-sided CI			(-1.8, 8.6)	(-5.0, 5.7)	(-5.2, 1.7)	(-2.8, 4.4)	(-5.3, 3.5)	(-1.3, 7.6)	(-8.6, 2.8)	(-3.6, 8.2)
Week 12										
n	52	52	19	19	61	60	31	31	13	13
Adjusted mean change from baseline (SE)	-0.6 (1.39)	-0.6 (1.42)	0.4 (2.51)	0.3 (2.55)	-1.9 (1.30)	-2.1 (1.34)	-4.0 (1.90)	-1.8 (1.93)	-2.2 (2.89)	2.2 (2.93)
Mean difference vs placebo (SE)			1.0 (2.84)	1.0 (2.89)	-1.4 (1.90)	-1.5 (1.95)	-3.5 (2.37)	-1.2 (2.41)	-1.6 (3.23)	2.9 (3.28)
95% 2-sided CI			(-4.6, 6.6)	(-4.7, 6.7)	(-5.1, 2.4)	(-5.3, 2.4)	(-8.2, 1.2)	(-6.0, 3.5)	(-8.0, 4.8)	(-3.6, 9.3)

Table continued on next page

	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
Hypertensive										
Baseline	504	502	171	171	482	482	359	358	187	187
n	133.4	129.9	136.8	133.9	134.2	130.3	132.3	127.9	134.8	130.5
Mean (SE)	(0.74)	(0.65)	(1.16)	(1.08)	(0.76)	(0.70)	(0.87)	(0.78)	(1.22)	(1.08)
Week 4										
n	503	501	171	171	480	480	357	356	187	187
Adjusted mean change from baseline (SE)	-0.4 (0.42)	-0.5 (0.44)	-0.3 (0.82)	-0.7 (0.86)	0.1 (0.43)	0.4 (0.45)	0.1 (0.53)	1.1 (0.55)	-1.3 (0.74)	-1.1 (0.77)
Mean difference vs placebo (SE)			0.2 (0.92)	-0.3 (0.96)	0.5 (0.60)	0.8 (0.63)	0.5 (0.68)	1.5 (0.71)	-0.9 (0.86)	-0.6 (0.90)
95% 2-sided CI			(-1.6, 2.0)	(-2.2, 1.6)	(-0.6, 1.7)	(-0.4, 2.1)	(-0.8, 1.9)	(0.1, 2.9)	(-2.6, 0.8)	(-2.4, 1.2)
Week 8										
n	471	468	165	165	453	453	347	346	182	182
Adjusted mean change from baseline (SE)	-0.3 (0.46)	0.1 (0.46)	-1.0 (0.87)	-1.6 (0.87)	-0.5 (0.47)	-0.3 (0.47)	-0.5 (0.56)	0.4 (0.56)	-1.4 (0.78)	0.0 (0.79)
Mean difference vs placebo (SE)			-0.7 (0.97)	-1.7 (0.98)	-0.3 (0.65)	-0.3 (0.65)	-0.2 (0.72)	0.3 (0.73)	-1.1 (0.91)	-0.1 (0.92)
95% 2-sided CI			(-2.6, 1.2)	(-3.6, 0.2)	(-1.6, 1.0)	(-1.6, 0.9)	(-1.6, 1.2)	(-1.1, 1.8)	(-2.9, 0.7)	(-1.8, 1.7)
Week 12										
n	451	449	163	163	435	435	337	336	171	171
Adjusted mean change from baseline (SE)	-0.4 (0.47)	0.2 (0.48)	-1.1 (0.88)	-1.3 (0.89)	0.2 (0.48)	0.7 (0.49)	-0.7 (0.57)	0.2 (0.58)	-0.2 (0.81)	0.2 (0.82)
Mean difference vs placebo (SE)			-0.8 (0.99)	-1.6 (1.01)	0.6 (0.67)	0.5 (0.68)	-0.4 (0.74)	-0.1 (0.75)	0.1 (0.94)	-0.0 (0.95)
95% 2-sided CI			(-2.7, 1.2)	(-3.5, 0.4)	(-0.7, 1.9)	(-0.9, 1.8)	(-1.8, 1.1)	(-1.5, 1.4)	(-1.7, 2.0)	(-1.9, 1.9)

Table 11 **Adjusted Mean Difference vs Placebo for Change (SE) from Baseline to Each Visit in DBP, by Hypertension Status 1, EU/NA OAB 12-week Phase 2/3 Population**

Parameter (mm Hg)	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Normotensive										
Baseline										
n	825	824	239	239	845	845	532	532	289	289
Mean (SE)	76.1 (0.31)	75.2 (0.29)	76.4 (0.58)	75.5 (0.57)	76.2 (0.30)	75.4 (0.31)	76.1 (0.38)	75.1 (0.36)	75.4 (0.48)	75.2 (0.46)
Week 4										
n	825	824	239	239	841	841	531	531	288	288
Adjusted mean change from baseline (SE)	-0.1 (0.18)	0.2 (0.19)	0.1 (0.38)	0.1 (0.39)	0.5 (0.18)	0.6 (0.19)	0.8 (0.24)	1.1 (0.24)	0.5 (0.33)	1.3 (0.34)
Mean difference vs placebo (SE)			0.2 (0.42)	-0.0 (0.43)	0.6 (0.26)	0.4 (0.27)	0.9 (0.30)	1.0 (0.31)	0.6 (0.38)	1.1 (0.39)
95% 2-sided CI			(-0.6, 1.0)	(-0.9, 0.8)	(0.1, 1.1)	(-0.1, 0.9)	(0.3, 1.5)	(0.3, 1.6)	(-0.2, 1.3)	(0.4, 1.9)
Week 8										
n	767	767	231	231	795	795	500	500	280	280
Adjusted mean change from baseline (SE)	0.1 (0.20)	0.4 (0.20)	-0.3 (0.40)	0.1 (0.41)	0.7 (0.20)	0.8 (0.20)	1.2 (0.25)	1.6 (0.26)	0.6 (0.35)	1.3 (0.35)
Mean difference vs placebo (SE)			-0.5 (0.45)	-0.3 (0.45)	0.6 (0.28)	0.5 (0.28)	1.1 (0.33)	1.2 (0.33)	0.4 (0.41)	0.9 (0.41)
95% 2-sided CI			(-1.3, 0.4)	(-1.1, 0.6)	(0.1, 1.1)	(-0.1, 1.0)	(0.5, 1.8)	(0.6, 1.8)	(-0.4, 1.2)	(0.1, 1.7)
Week 12										
n	749	749	224	224	770	769	489	489	267	267
Adjusted mean change from baseline (SE)	0.4 (0.21)	0.6 (0.21)	0.1 (0.41)	0.1 (0.42)	0.7 (0.20)	0.9 (0.20)	0.8 (0.26)	1.5 (0.26)	0.9 (0.36)	1.7 (0.36)
Mean difference vs placebo (SE)			-0.4 (0.46)	-0.6 (0.46)	0.3 (0.29)	0.3 (0.29)	0.3 (0.33)	0.9 (0.34)	0.5 (0.42)	1.0 (0.42)
95% 2-sided CI			(-1.3, 0.5)	(-1.5, 0.3)	(-0.3, 0.9)	(-0.3, 0.8)	(-0.3, 1.0)	(0.2, 1.5)	(-0.4, 1.3)	(0.2, 1.8)
Past history of hypertension										
Baseline										
n	54	54	20	20	65	65	33	33	15	15
Mean (SE)	82.7 (1.33)	79.6 (1.21)	76.9 (2.43)	74.8 (2.71)	84.5 (1.07)	83.0 (1.29)	81.0 (2.03)	80.2 (1.87)	81.6 (2.14)	80.9 (2.48)
Week 4										
n	54	54	20	20	64	64	33	33	15	15
Adjusted mean change from baseline (SE)	-0.3 (0.89)	-0.4 (0.86)	-1.6 (1.62)	-2.9 (1.58)	-1.6 (0.83)	-1.2 (0.81)	2.2 (1.20)	1.7 (1.17)	-2.6 (1.80)	1.0 (1.76)
Mean difference vs placebo (SE)			-1.3 (1.83)	-2.5 (1.78)	-1.3 (1.21)	-0.8 (1.18)	2.5 (1.51)	2.1 (1.47)	-2.4 (2.03)	1.4 (1.98)
95% 2-sided CI			(-4.9, 2.3)	(-6.0, 1.1)	(-3.7, 1.1)	(-3.1, 1.6)	(-0.5, 5.5)	(-0.8, 5.0)	(-6.4, 1.6)	(-2.5, 5.3)
Week 8										
n	51	51	19	19	64	64	30	30	15	15
Adjusted mean change from baseline (SE)	0.7 (0.88)	0.2 (0.89)	-1.1 (1.60)	-3.8 (1.63)	-0.5 (0.80)	0.3 (0.82)	1.6 (1.20)	2.2 (1.22)	-0.6 (1.75)	1.4 (1.78)
Mean difference vs placebo (SE)			-1.8 (1.81)	-4.0 (1.83)	-1.2 (1.19)	0.2 (1.21)	1.0 (1.50)	2.0 (1.52)	-1.3 (1.97)	1.2 (2.00)
95% 2-sided CI			(-5.3, 1.8)	(-7.6, -0.4)	(-3.5, 1.2)	(-2.2, 2.5)	(-2.0, 3.9)	(-1.0, 5.0)	(-5.1, 2.6)	(-2.8, 5.2)
Week 12										
n	52	52	19	19	61	60	31	31	13	13
Adjusted mean change from baseline (SE)	-0.1 (0.91)	-0.7 (0.96)	-1.4 (1.67)	-3.4 (1.74)	-0.9 (0.85)	-0.7 (0.90)	1.8 (1.24)	1.3 (1.30)	-0.3 (1.88)	2.4 (1.98)
Mean difference vs placebo (SE)			-1.3 (1.88)	-2.7 (1.97)	-0.9 (1.24)	-0.1 (1.32)	1.9 (1.55)	2.0 (1.63)	-0.2 (2.11)	3.0 (2.22)
95% 2-sided CI			(-5.1, 2.4)	(-6.6, 1.2)	(-3.3, 1.6)	(-2.7, 2.5)	(-1.2, 4.9)	(-1.2, 5.2)	(-4.3, 4.0)	(-1.4, 7.4)

Table continued on next page

	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
Hypertensive										
Baseline										
n	504	502	171	171	482	482	358	358	187	187
Mean (SE)	78.9 (0.43)	75.5 (0.40)	80.8 (0.76)	76.8 (0.75)	78.8 (0.41)	75.5 (0.40)	79.4 (0.45)	75.6 (0.44)	79.0 (0.65)	75.6 (0.66)
Week 4										
n	503	501	171	171	480	480	356	356	187	187
Adjusted mean change from baseline (SE)	-0.7 (0.25)	-0.4 (0.27)	-0.8 (0.49)	-0.3 (0.52)	-0.1 (0.25)	0.2 (0.27)	0.0 (0.31)	0.3 (0.33)	0.1 (0.44)	0.4 (0.47)
Mean difference vs placebo (SE)			-0.1 (0.54)	0.0 (0.58)	0.5 (0.35)	0.6 (0.38)	0.7 (0.40)	0.7 (0.43)	0.8 (0.51)	0.8 (0.54)
95% 2-sided CI			(-1.2, 0.9)	(-1.1, 1.2)	(-0.2, 1.2)	(-0.2, 1.3)	(-0.1, 1.5)	(-0.1, 1.5)	(-0.2, 1.8)	(-0.3, 1.8)
Week 8										
n	471	468	165	165	453	453	346	346	182	182
Adjusted mean change from baseline (SE)	-0.4 (0.27)	-0.3 (0.28)	-1.4 (0.52)	-0.7 (0.54)	-0.6 (0.28)	-0.2 (0.29)	-0.5 (0.33)	0.4 (0.34)	-0.6 (0.47)	0.8 (0.48)
Mean difference vs placebo (SE)			-1.0 (0.58)	-0.5 (0.60)	-0.1 (0.39)	0.1 (0.40)	-0.1 (0.43)	0.7 (0.45)	-0.2 (0.54)	1.1 (0.56)
95% 2-sided CI			(-2.1, 0.2)	(-1.6, 0.7)	(-0.9, 0.6)	(-0.7, 0.9)	(-0.9, 0.8)	(-0.2, 1.6)	(-1.2, 0.9)	(0.0, 2.2)
Week 12										
n	451	449	163	163	435	435	336	336	171	171
Adjusted mean change from baseline (SE)	-0.5 (0.28)	-0.1 (0.29)	-0.6 (0.52)	-0.2 (0.55)	-0.1 (0.28)	0.5 (0.30)	-0.7 (0.34)	0.1 (0.35)	0.2 (0.48)	0.7 (0.50)
Mean difference vs placebo (SE)			-0.1 (0.59)	-0.2 (0.62)	0.5 (0.40)	0.5 (0.41)	-0.1 (0.44)	0.2 (0.46)	0.7 (0.56)	0.8 (0.58)
95% 2-sided CI			(-1.3, 1.1)	(-1.4, 1.0)	(-0.3, 1.3)	(-0.3, 1.4)	(-1.0, 0.7)	(-0.7, 1.1)	(-0.4, 1.8)	(-0.4, 1.9)

Finally, figures F-7, F-8 and F-9 below from study ISN 178-PK-016 show that there are virtually no differences in the increase of pulse rate, DBP, or SBP as a function of mirabegron exposure between normotensive patients and hypertensive patients or patients with past history of hypertension

For a discussion of differential categorical SBP/DBP event rates based on hypertensive status, as well as an analysis of potentially clinically significant (PCS) blood pressure changes, see question 4.

Figure F- 7 Individual morning and afternoon pulse rate changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The orange and blue solid lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.

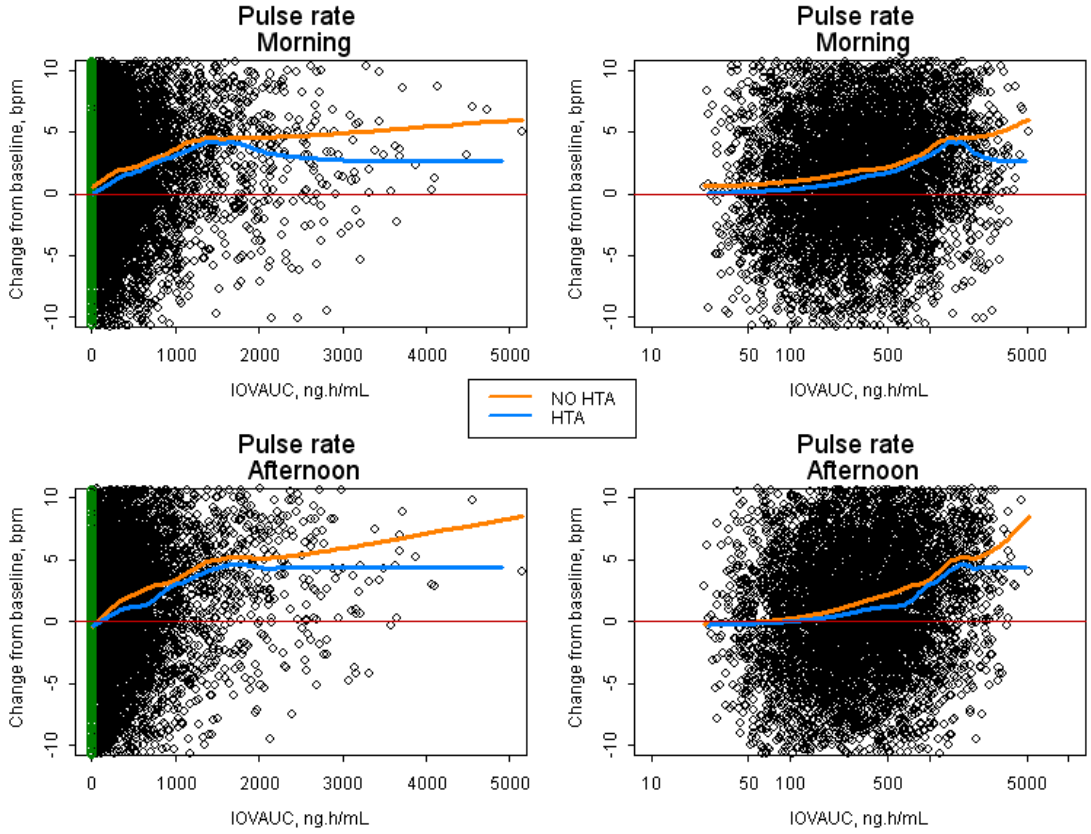


Figure F- 8 Individual morning and afternoon diastolic blood pressure (DBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The solid orange and blue lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.

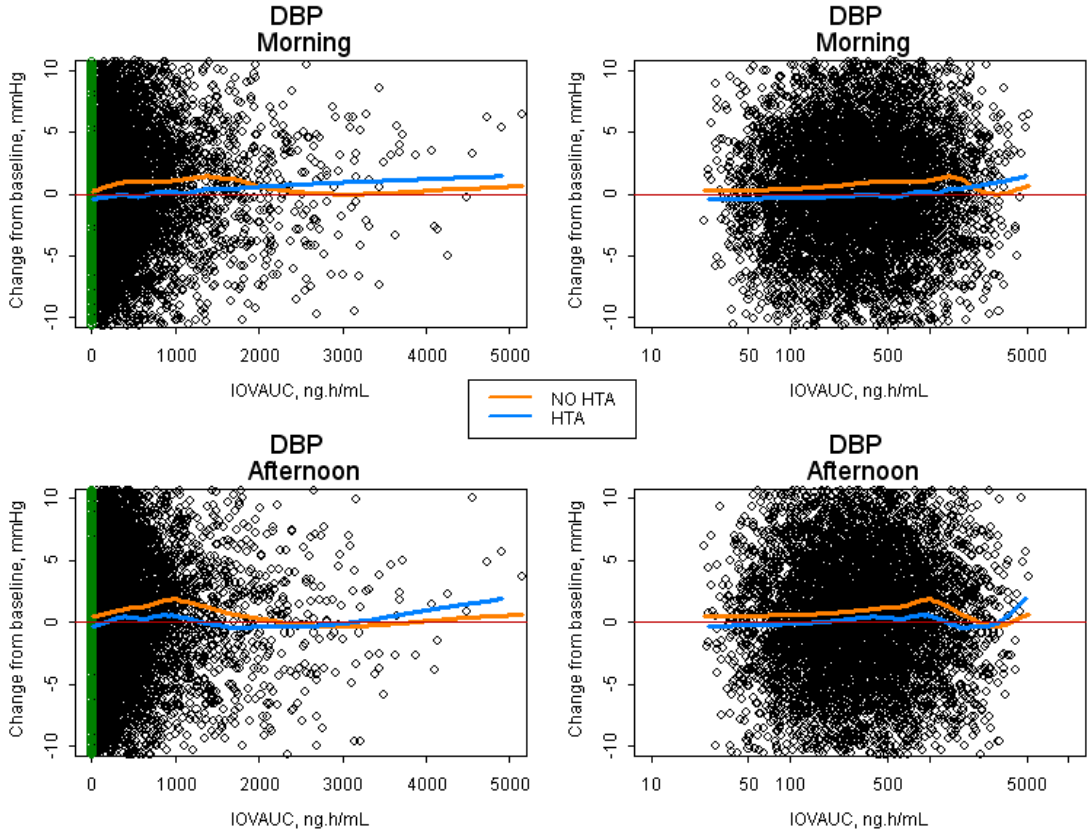
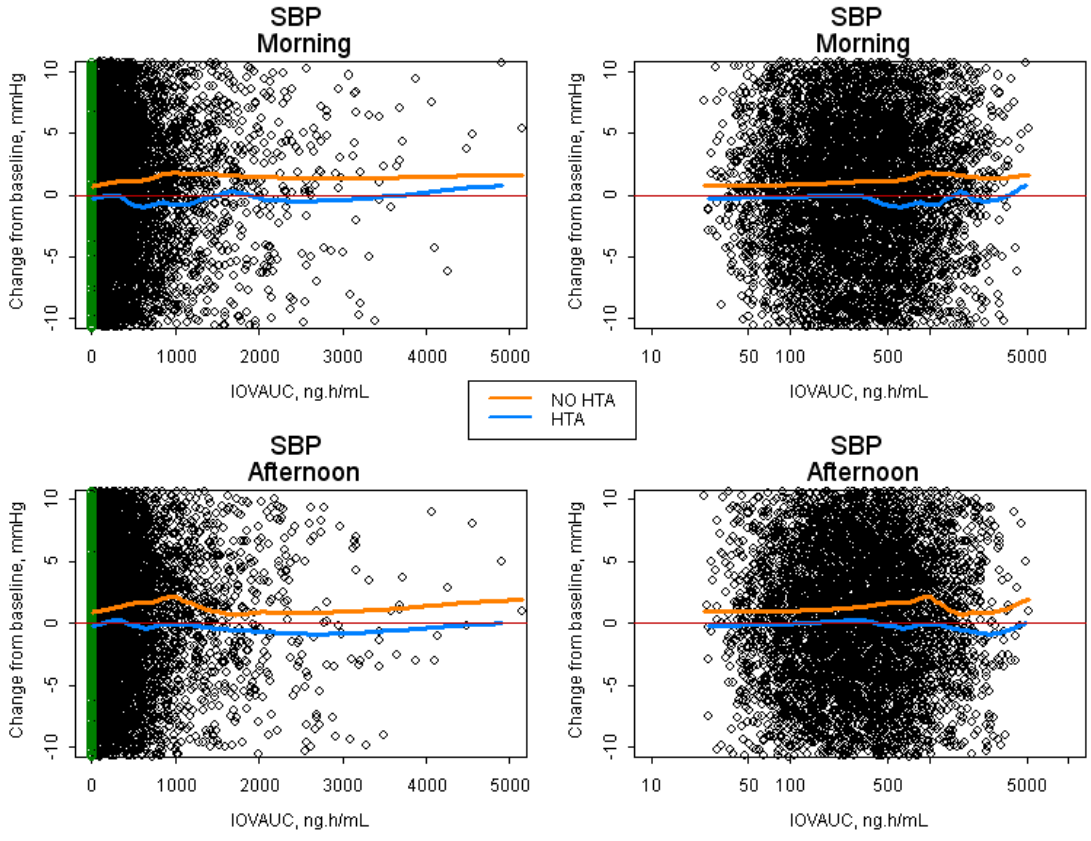


Figure F- 9 Individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The solid orange and blue lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.



4. **Please refer to Table 22 page 70 and Figure 15 page 93 of report. Please provide your assessment of the sponsor's categorical analysis based upon proportions of blood pressure outliers?**

For convenience of reference, Table 22 from the sponsor's CRR is reproduced below:

Table 22. Patients Whose AM or PM SBP or DBP Measurements from the Patient Diary Met Selected Criteria, EU/NA OAB 12-week Phase 3 Population

Parameter, n/n (%) of Patients	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
SBP					
AM	**(n = 1380)**	**(n = 432)**	**(n = 1375)**	**(n = 929)**	**(n = 495)**
Final visit					
Change from baseline ε 15 mm Hg	70/1329 (5.3%)	21/410 (5.1%)	89/1327 (6.7%)	53/891 (5.9%)	17/476 (3.6%)
2 consecutive postbaseline visits					
Change from baseline ≥ 2 mm Hg	438/1242	128/396 (32.3%)	483/1247 (38.7%)	315/852 (37.0%)	142/463 (30.7%)
Change from baseline ≥ 5 mm Hg	(35.3%)	78/396 (19.7%)	303/1247 (24.3%)	204/852 (23.9%)	83/463 (17.9%)
Change from baseline ε 10 mm Hg	263/1242	34/396 (8.6%)	100/1247 (8.0%)	63/852 (7.4%)	26/463 (5.6%)
Change from baseline ε 15 mm Hg	(21.2%)	6/396 (1.5%)	28/1247 (2.2%)	20/852 (2.3%)	7/463 (1.5%)
Change from baseline ε 20 mm Hg	94/1242 (7.6%)	2/396 (0.5%)	15/1247 (1.2%)	10/852 (1.2%)	3/463 (0.6%)
PM	**(n = 1380)**	**(n = 432)**	**(n = 1375)**	**(n = 929)**	**(n = 495)**
Final visit					
Change from baseline ε 15 mm Hg	86/1326 (6.5%)	23/410 (5.6%)	94/1327 (7.1%)	69/890 (7.8%)	35/476 (7.4%)
2 consecutive postbaseline visits					
Change from baseline ≥ 2 mm Hg	444/1239	118/396 (29.8%)	448/1247 (35.9%)	362/851 (42.5%)	167/463 (36.1%)
Change from baseline ≥ 5 mm Hg	(35.8%)	74/396 (18.7%)	307/1247 (24.6%)	240/851 (28.2%)	105/463 (22.7%)
Change from baseline ε 10 mm Hg	285/1239	26/396 (6.6%)	109/1247 (8.7%)	85/851 (10.0%)	41/463 (8.9%)
Change from baseline ε 15 mm Hg	(23.0%)	8/396 (2.0%)	31/1247 (2.5%)	25/851 (2.9%)	11/463 (2.4%)
Change from baseline ε 20 mm Hg	101/1239 (8.2%)	4/396 (1.0%)	11/1247 (0.9%)	9/851 (1.1%)	4/463 (0.9%)
DBP					
AM	**(n = 1380)**	**(n = 432)**	**(n = 1375)**	**(n = 929)**	**(n = 495)**
Final visit					
Change from baseline ε 10 mm Hg	61/1329 (4.6%)	17/410 (4.1%)	88/1327 (6.6%)	53/890 (6.0%)	25/476 (5.3%)
2 consecutive postbaseline visits					
Change from baseline ε 2 mm Hg	329/1242 (26.5%)	99/396 (25.0%)	410/1247 (32.9%)	292/851 (34.3%)	151/463 (32.6%)
Change from baseline ε 5 mm Hg	150/1242 (12.1%)	47/396 (11.9%)	180/1247 (14.4%)	122/851 (14.3%)	61/463 (13.2%)
Change from baseline ε 10 mm Hg	29/1242 (2.3%)	5/396 (1.3%)	31/1247 (2.5%)	25/851 (2.9%)	8/463 (1.7%)
Change from baseline ε 15 mm Hg	3/1242 (0.2%)	1/396 (0.3%)	2/1247 (0.2%)	5/851 (0.6%)	2/463 (0.4%)
PM	**(n = 1380)**	**(n = 432)**	**(n = 1375)**	**(n = 929)**	**(n = 495)**
Final visit					
Change from baseline ε 10 mm Hg	71/1326 (5.4%)	18/410 (4.4%)	91/1327 (6.9%)	78/890 (8.8%)	38/476 (8.0%)
2 consecutive postbaseline visits					
Change from baseline ε 2 mm Hg	374/1239 (30.2%)	99/396 (25.0%)	393/1247 (31.5%)	319/851 (37.5%)	186/463 (40.2%)
Change from baseline ε 5 mm Hg	166/1239 (13.4%)	43/396 (10.9%)	193/1247 (15.5%)	173/851 (20.3%)	86/463 (18.6%)
Change from baseline ε 10 mm Hg	26/1239 (2.1%)	9/396 (2.3%)	31/1247 (2.5%)	38/851 (4.5%)	12/463 (2.6%)
Change from baseline ε 15 mm Hg	0/1239	1/396 (0.3%)	5/1247 (0.4%)	5/851 (0.6%)	1/463 (0.2%)

Categorical changes from baseline displayed in Table 22 above show numerically higher percentages of patients at the final visit with SBP and DBP elevations on 50mg mirabegron than for patients on tolterodine, but the same is true for placebo. This may be an artifact of the program design, in that all of the phase III tolterodine data in this table is generated from European study 046, while the placebo and mirabegron data columns are an integration of data from 046 and 047, the latter of which includes

data from the US. Thus, comparing 50mg mirabegron only to placebo, the differences in final visit 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 the some of the tolterodine PM elevation rates are higher than for 50mg mirabegron.

To dissect this data more thoroughly, we went back to the 046 dataset to look at within-study differences of these categorical SBP/DBP elevation rates between placebo, mirabegron, and tolterodine, for the overall patient population, normotensives, and hypertensives (Hypertensive Status 1 definitions), split by AM and PM, data which is shown below in tables 69 – 72 from the 046 FSR:

Table 69 Incidence of Patients Whose AM Systolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	**(n=494)**	**(n=493)**	**(n=496)**	**(n=495)**
Final Visit				
Change from baseline ≥ 15 mm Hg	26/481 (5.4%)	28/474 (5.9%)	27/479 (5.6%)	17/476 (3.6%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	14/449 (3.1%)	10/437 (2.3%)	13/443 (2.9%)	8/436 (1.8%)
Change from baseline ≥ 15 mm Hg	5/449 (1.1%)	3/437 (0.7%)	5/443 (1.1%)	2/436 (0.5%)
Change from baseline ≥ 20 mm Hg	4/449 (0.9%)	2/437 (0.5%)	3/443 (0.7%)	2/436 (0.5%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	40/464 (8.6%)	27/450 (6.0%)	35/456 (7.7%)	26/461 (5.6%)
Change from baseline ≥ 15 mm Hg	16/464 (3.4%)	10/450 (2.2%)	14/456 (3.1%)	7/461 (1.5%)
Change from baseline ≥ 20 mm Hg	8/464 (1.7%)	6/450 (1.3%)	7/456 (1.5%)	3/461 (0.7%)
Normotensive	**(n=298)**	**(n=321)**	**(n=313)**	**(n=300)**
Final Visit				
Change from baseline ≥ 15 mm Hg	12/288 (4.2%)	15/312 (4.8%)	19/302 (6.3%)	7/289 (2.4%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	5/270 (1.9%)	7/288 (2.4%)	9/276 (3.3%)	2/265 (0.8%)
Change from baseline ≥ 15 mm Hg	1/270 (0.4%)	1/288 (0.3%)	5/276 (1.8%)	1/265 (0.4%)
Change from baseline ≥ 20 mm Hg	1/270 (0.4%)	1/288 (0.3%)	3/276 (1.1%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	21/276 (7.6%)	16/296 (5.4%)	22/285 (7.7%)	10/279 (3.6%)
Change from baseline ≥ 15 mm Hg	6/276 (2.2%)	6/296 (2.0%)	8/285 (2.8%)	2/279 (0.7%)
Change from baseline ≥ 20 mm Hg	2/276 (0.7%)	3/296 (1.0%)	4/285 (1.4%)	1/279 (0.4%)
Hypertensive Population	**(n=196)**	**(n=172)**	**(n=183)**	**(n=195)**
Final Visit				
Change from baseline ≥ 15 mm Hg	14/193 (7.3%)	13/162 (8.0%)	8/177 (4.5%)	10/187 (5.3%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	9/179 (5.0%)	3/149 (2.0%)	4/167 (2.4%)	6/171 (3.5%)
Change from baseline ≥ 15 mm Hg	4/179 (2.2%)	2/149 (1.3%)	0	1/171 (0.6%)
Change from baseline ≥ 20 mm Hg	3/179 (1.7%)	1/149 (0.7%)	0	1/171 (0.6%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	19/188 (10.1%)	11/154 (7.1%)	13/171 (7.6%)	16/182 (8.8%)
Change from baseline ≥ 15 mm Hg	10/188 (5.3%)	4/154 (2.6%)	6/171 (3.5%)	5/182 (2.7%)
Change from baseline ≥ 20 mm Hg	6/188 (3.2%)	3/154 (1.9%)	3/171 (1.8%)	2/182 (1.1%)

Table 70 Incidence of Patients Whose PM Systolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	**(n=494)**	**(n=493)**	**(n=496)**	**(n=495)**
Final Visit				
Change from baseline ≥ 15 mm Hg	34/479 (7.1%)	24/474 (5.1%)	37/478 (7.7%)	33/476 (6.9%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	11/447 (2.5%)	18/437 (4.1%)	21/442 (4.8%)	16/436 (3.7%)
Change from baseline ≥ 15 mm Hg	2/447 (0.4%)	5/437 (1.1%)	7/442 (1.6%)	4/436 (0.9%)
Change from baseline ≥ 20 mm Hg	1/447 (0.2%)	1/437 (0.2%)	3/442 (0.7%)	2/436 (0.5%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	36/462 (7.8%)	38/450 (8.4%)	46/455 (10.1%)	41/461 (8.9%)
Change from baseline ≥ 15 mm Hg	8/462 (1.7%)	9/450 (2.0%)	16/455 (3.5%)	11/461 (2.4%)
Change from baseline ≥ 20 mm Hg	2/462 (0.4%)	5/450 (1.1%)	8/455 (1.8%)	4/461 (0.9%)
Normotensive	**(n=298)**	**(n=321)**	**(n=313)**	**(n=300)**
Final Visit				
Change from baseline ≥ 15 mm Hg	16/288 (5.6%)	15/312 (4.8%)	21/302 (7.0%)	12/289 (4.2%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	2/270 (0.7%)	11/288 (3.8%)	13/276 (4.7%)	7/265 (2.6%)
Change from baseline ≥ 15 mm Hg	0	4/288 (1.4%)	3/276 (1.1%)	1/265 (0.4%)
Change from baseline ≥ 20 mm Hg	0	1/288 (0.3%)	2/276 (0.7%)	0
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	15/276 (5.4%)	26/296 (8.8%)	32/285 (11.2%)	18/279 (6.5%)
Change from baseline ≥ 15 mm Hg	1/276 (0.4%)	7/296 (2.4%)	9/285 (3.2%)	6/279 (2.2%)
Change from baseline ≥ 20 mm Hg	0	4/296 (1.4%)	5/285 (1.8%)	1/279 (0.4%)
Hypertensive Population	**(n=196)**	**(n=172)**	**(n=183)**	**(n=195)**
Final Visit				
Change from baseline ≥ 15 mm Hg	18/191 (9.4%)	9/162 (5.6%)	16/176 (9.1%)	21/187 (11.2%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	9/177 (5.1%)	7/149 (4.7%)	8/166 (4.8%)	9/171 (5.3%)
Change from baseline ≥ 15 mm Hg	2/177 (1.1%)	1/149 (0.7%)	4/166 (2.4%)	3/171 (1.8%)
Change from baseline ≥ 20 mm Hg	1/177 (0.6%)	0	1/166 (0.6%)	2/171 (1.2%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	21/186 (11.3%)	12/154 (7.8%)	14/170 (8.2%)	23/182 (12.6%)
Change from baseline ≥ 15 mm Hg	7/186 (3.8%)	2/154 (1.3%)	7/170 (4.1%)	5/182 (2.7%)
Change from baseline ≥ 20 mm Hg	2/186 (1.1%)	1/154 (0.6%)	3/170 (1.8%)	3/182 (1.6%)

Table 71 Incidence of Patients Whose AM Diastolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	**(n=494)**	**(n=493)**	**(n=496)**	**(n=495)**
Final Visit				
Change from baseline ≥ 10 mm Hg	21/481 (4.4%)	26/474 (5.5%)	23/478 (4.8%)	25/476 (5.3%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	29/449 (6.5%)	27/437 (6.2%)	34/442 (7.7%)	28/436 (6.4%)
Change from baseline ≥ 10 mm Hg	5/449 (1.1%)	4/437 (0.9%)	7/442 (1.6%)	2/436 (0.5%)
Change from baseline ≥ 15 mm Hg	0	0	2/442 (0.5%)	1/436 (0.2%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	65/464 (14.0%)	65/450 (14.4%)	70/455 (15.4%)	60/461 (13.0%)
Change from baseline ≥ 10 mm Hg	14/464 (3.0%)	6/450 (1.3%)	12/455 (2.6%)	7/461 (1.5%)
Change from baseline ≥ 15 mm Hg	2/464 (0.4%)	0	3/455 (0.7%)	2/461 (0.4%)
Normotensive Population	**(n=298)**	**(n=321)**	**(n=313)**	**(n=300)**
Final Visit				
Change from baseline ≥ 10 mm Hg	13/288 (4.5%)	19/312 (6.1%)	19/302 (6.3%)	16/289 (5.5%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	17/270 (6.3%)	19/288 (6.6%)	24/276 (8.7%)	17/265 (6.4%)
Change from baseline ≥ 10 mm Hg	3/270 (1.1%)	2/288 (0.7%)	6/276 (2.2%)	1/265 (0.4%)
Change from baseline ≥ 15 mm Hg	0	0	2/276 (0.7%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	37/276 (13.4%)	50/296 (16.9%)	45/285 (15.8%)	36/279 (12.9%)
Change from baseline ≥ 10 mm Hg	8/276 (2.9%)	4/296 (1.4%)	9/285 (3.2%)	5/279 (1.8%)
Change from baseline ≥ 15 mm Hg	1/276 (0.4%)	0	3/285 (1.1%)	2/279 (0.7%)
Hypertensive Population	**(n=196)**	**(n=172)**	**(n=183)**	**(n=195)**
Final Visit				
Change from baseline ≥ 10 mm Hg	8/193 (4.1%)	7/162 (4.3%)	4/176 (2.3%)	9/187 (4.8%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	12/179 (6.7%)	8/149 (5.4%)	10/166 (6.0%)	11/171 (6.4%)
Change from baseline ≥ 10 mm Hg	2/179 (1.1%)	2/149 (1.3%)	1/166 (0.6%)	1/171 (0.6%)
Change from baseline ≥ 15 mm Hg	0	0	0	0
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	28/188 (14.9%)	15/154 (9.7%)	25/170 (14.7%)	24/182 (13.2%)
Change from baseline ≥ 10 mm Hg	6/188 (3.2%)	2/154 (1.3%)	3/170 (1.8%)	2/182 (1.1%)
Change from baseline ≥ 15 mm Hg	1/188 (0.5%)	0	0	0

Table 72 Incidence of Patients Whose PM Diastolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	**(n=494)**	**(n=493)**	**(n=496)**	**(n=495)**
Final Visit				
Change from baseline ≥ 10 mm Hg	23/479 (4.8%)	29/474 (6.1%)	40/478 (8.4%)	37/476 (7.8%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	20/447 (4.5%)	21/437 (4.8%)	41/442 (9.3%)	43/436 (9.9%)
Change from baseline ≥ 10 mm Hg	3/447 (0.7%)	0	6/442 (1.4%)	7/436 (1.6%)
Change from baseline ≥ 15 mm Hg	0	0	3/442 (0.7%)	1/436 (0.2%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	51/462 (11.0%)	68/450 (15.1%)	94/455 (20.7%)	85/461 (18.4%)
Change from baseline ≥ 10 mm Hg	8/462 (1.7%)	9/450 (2.0%)	18/455 (4.0%)	12/461 (2.6%)
Change from baseline ≥ 15 mm Hg	0	0	4/455 (0.9%)	1/461 (0.2%)
Normotensive Population	**(n=298)**	**(n=321)**	**(n=313)**	**(n=300)**
Final Visit				
Change from baseline ≥ 10 mm Hg	14/288 (4.9%)	21/312 (6.7%)	28/302 (9.3%)	21/289 (7.3%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	11/270 (4.1%)	15/288 (5.2%)	29/276 (10.5%)	27/265 (10.2%)
Change from baseline ≥ 10 mm Hg	0	0	5/276 (1.8%)	2/265 (0.8%)
Change from baseline ≥ 15 mm Hg	0	0	3/276 (1.1%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	30/276 (10.9%)	54/296 (18.2%)	61/285 (21.4%)	51/279 (18.3%)
Change from baseline ≥ 10 mm Hg	3/276 (1.1%)	6/296 (2.0%)	12/285 (4.2%)	5/279 (1.8%)
Change from baseline ≥ 15 mm Hg	0	0	3/285 (1.1%)	1/279 (0.4%)
Hypertensive Population	**(n=196)**	**(n=172)**	**(n=183)**	**(n=195)**
Final Visit				
Change from baseline ≥ 10 mm Hg	9/191 (4.7%)	8/162 (4.9%)	12/176 (6.8%)	16/187 (8.6%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	9/177 (5.1%)	6/149 (4.0%)	12/166 (7.2%)	16/171 (9.4%)
Change from baseline ≥ 10 mm Hg	3/177 (1.7%)	0	1/166 (0.6%)	5/171 (2.9%)
Change from baseline ≥ 15 mm Hg	0	0	0	0
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 5 mm Hg	21/186 (11.3%)	14/154 (9.1%)	33/170 (19.4%)	34/182 (18.7%)
Change from baseline ≥ 10 mm Hg	5/186 (2.7%)	3/154 (1.9%)	6/170 (3.5%)	7/182 (3.8%)
Change from baseline ≥ 15 mm Hg	0	0	1/170 (0.6%)	0

So within trial 046, from which all of the comparative phase III tolterodine data is generated, the following observations are made:

- AM SBP
  - Rates of final visit categorical elevations for mirabegron are numerically higher than for tolterodine in normotensives and hypertensives, but the differential rates are small. The same is true for placebo.
  - Notably, hypertensive patients on placebo demonstrate higher "consecutive" categorical event rates compared to their 50 mg mirabegron-treated counterparts

- PM SBP
  - There are numerically higher final visit event rates for mirabegron vs tolterodine in normotensives, but numerically higher final visit event rates for tolterodine in hypertensives, but the differential rates are small.
  - Again, hypertensives on placebo demonstrate higher "consecutive" categorical event rates compared to their 50 mg mirabegron-treated counterparts

- AM DBP
  - Similar final visit event rates between placebo, mirabegron, and tolterodine in normotensives
  - Numerically lower categorical event rates in hypertensives on mirabegron as compared to placebo

- PM DBP
  - Lower final visit event rates for 50 mg mirabegron in normotensives and hypertensives as compared to tolterodine, with generally lower categorical events for mirabegron in both subsets
  - Both mirabegron and tolterodine with numerically higher categorical event rates compared to placebo, but the differences are small.

Given the small differences in the categorical event rates above, which may not be true differences, the graphical displays of individual changes from baseline as a function of exposure for the integrated phase III safety population is instructive. Note that Figure 15 of the sponsor's CRR that is specifically pointed out in the consult request is identical to Figure 23 of the study ISN 178-PK-016 FSR, which is shown above under question 1, and it displays individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047]. Note that this same type of graphical display is included in question 1 above for the DBP changes from baseline as well. As discussed in question 1, there are no trends for change from baseline in DBP or SBP with increasing exposure to mirabegron (see question 1, figure 14 and figure 23, respectively).

Finally, potentially clinically significant blood pressure findings were assessed for both the 12-week phase III and the long-term controlled EU/NA populations, as shown in Tables 28 and 29 below (from CRR Appendix 4). The occurrence of these events was comparable between all of the treatment groups.

Table 28 **Patients Meeting PCS Criteria for AM or PM SBP and DBP Measured by Patient's Diary, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1**

Parameter	Time Point	Placebo (n = 1380)	Mirabegron 25 mg (n = 432)	Mirabegron 50 mg (n = 1375)	Mirabegron 100 mg (n = 929)	Tolterodine ER 4 mg (n = 495)
Normotensive†		**(n = 857)**	**(n = 250)**	**(n = 873)**	**(n = 555)**	**(n = 300)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	1/825 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
	PM	0/824	0/239	1/845 (0.1%)	0/532	0/289
Any visit	AM	1/825 (0.1%)	0/239	2/845 (0.2%)	1/532 (0.2%)	0/289
	PM	0/824	0/239	1/845 (0.1%)	0/532	0/289
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/825 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
	PM	1/824 (0.1%)	0/239	0/845	1/532 (0.2%)	0/289
Any visit	AM	1/825 (0.1%)	0/239	2/845 (0.2%)	1/532 (0.2%)	0/289
	PM	1/824 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
Past history of hypertension†		**(n = 58)**	**(n = 22)**	**(n = 67)**	**(n = 35)**	**(n = 15)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	0/54	0/20	0/65	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Any visit	AM	0/54	0/20	1/65 (1.5%)	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/54 (1.9%)	0/20	0/65	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Any visit	AM	1/54 (1.9%)	0/20	1/65 (1.5%)	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Hypertensive†		**(n = 523)**	**(n = 182)**	**(n = 502)**	**(n = 374)**	**(n = 195)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	1/504 (0.2%)	1/171 (0.6%)	1/482 (0.2%)	0/359	1/187 (0.5%)
	PM	0/502	0/171	0/482	0/358	0/187
Any visit	AM	3/504 (0.6%)	1/171 (0.6%)	3/482 (0.6%)	1/359 (0.3%)	1/187 (0.5%)
	PM	0/502	1/171 (0.6%)	1/482 (0.2%)	0/358	0/187
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/504 (0.2%)	0/171	1/482 (0.2%)	0/358	0/187
	PM	0/502	0/171	0/482	1/358 (0.3%)	0/187
Any visit	AM	1/504 (0.2%)	0/171	1/482 (0.2%)	1/358 (0.3%)	0/187
	PM	0/502	0/171	1/482 (0.2%)	1/358 (0.3%)	0/187

Table 29 **Patients Meeting PCS Criteria for AM or PM SBP or DBP Measured by Patient Diary, EU/NA Long-term Controlled Population, Hypertension status 1**

Visit	Time Point	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Tolterodine ER 4 mg (n = 812)
Normotensive†		**(n = 488)**	**(n = 509)**	**(n = 478)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	1/474 (0.2%)	0	0
Any visit	AM	0	0	1/469 (0.2%)
	PM	1/474 (0.2%)	0	1/469 (0.2%)
Past history of hypertension†		**(n = 33)**	**(n = 52)**	**(n = 43)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
Hypertensive†		**(n = 324)**	**(n = 311)**	**(n = 334)**
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	1/317 (0.3%)	1/304 (0.3%)	3/324 (0.9%)
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	1/304 (0.3%)	1/324 (0.3%)
	PM	0	0	2/324 (0.6%)
Any visit	AM	0	1/304 (0.3%)	5/324 (1.5%)
	PM	1/315 (0.3%)	0	3/324 (0.9%)

CARDIOVASCULAR RISK

ASSESSMENT

D

Background:

The Division of Reproductive and Urologic Products (DRUP) consulted us to provide an assessment of the cardiovascular risk associated with the increases in systolic blood pressure for mirabegron. The Division of Cardiovascular and Renal Products (DCRP) provided advice to the sponsor[1] with regard to the cardiovascular risk assessment using the Cox Proportional Hazards model described by D'Agostino et al[2]. In the current document, the cardiovascular risk projection based on the blood pressure data pooled from 3 Phase III trials of 12 weeks duration (178-CL-046, 178-CL-047 and 178-CL-074) is presented. In an attempt to characterize the blood pressure effects of mirabegron, Study 178-CL-031 and Study 178-Cl-077 (Thorough QT study) are evaluated[3]. The changes in the projected cardiovascular risk based on the blood pressure effect derived from the TQT study are also performed.

Key Questions:

1) **What is the effect of mirabegron on blood pressure?**

Based on the results of the phase I studies Study CL-178-031, mirabegron demonstrates an exposure-dependent increase in blood pressure (systolic as well as diastolic) as shown in the Figure 1 below.

[1] *Teleconference dated 02/09/2012 and 03/01/2012*

[2] *General Cardiovscular Risk Profile fo Use in Primary Care: The Framingham Heart Study. Ralph B. D'Agostino et al. Circulation 2008;117;743-753*

[3] *Analyses performed by Jiang Liu, Ph.D., Pharmacometrics Reviewer, OCP. For details see the Clinical Pharmacology AC Background Document.*

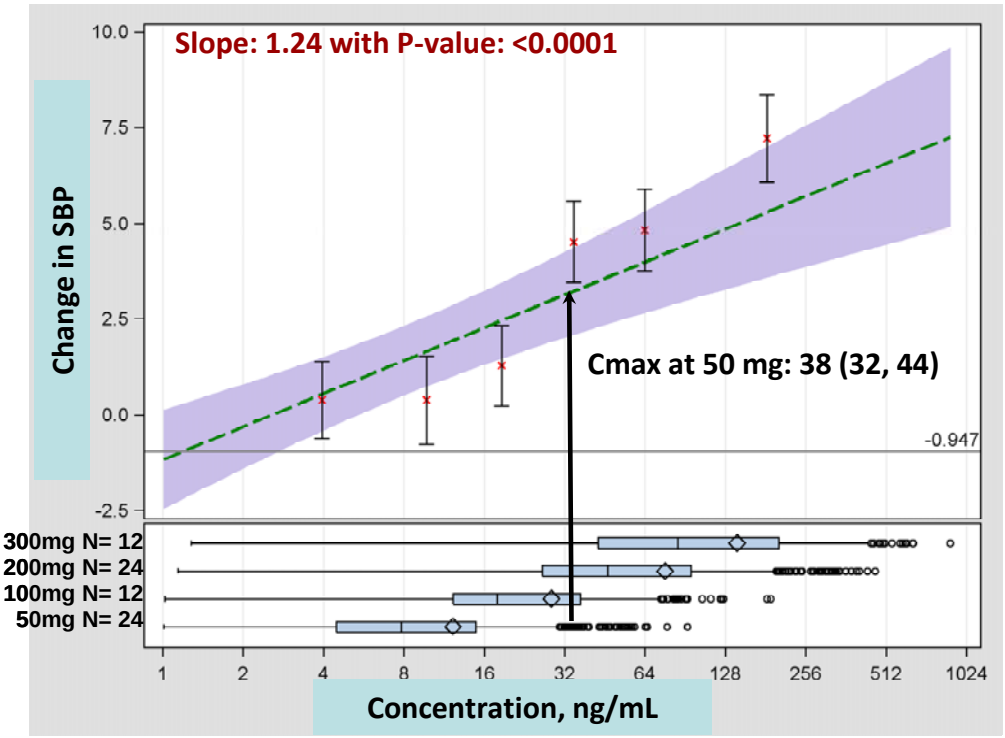


Figure 1: A concentration-dependent increase in blood pressure is observed over the range of doses studied in Study CL-178-031. ***For the purpose of plotting, the data are divided in to 6 equal bins of observed mirabegron concentration. The red cross (x) and the associated error bars represent the mean change in systolic blood pressure (SBP) corresponding to the median concentration for each bin and the corresponding 95% confidence intervals. The dashed green line represents regression mean for the entire data and the purple band is the associated 95% confidence interval. (Source: OCP AC Background Document)***

The increase in blood pressure was similar between younger subjects (18 – 55 years) and older subjects (65 – 77 years) after correction for the placebo effects[3]. The maximum blood pressure effects coincided with the peak concentration following the administration of mirabegron. A consistent dose-response relationship was also noted in the TQT study (Study 178-CL-077) at steady-state (Day 14) as shown in Figure 2.

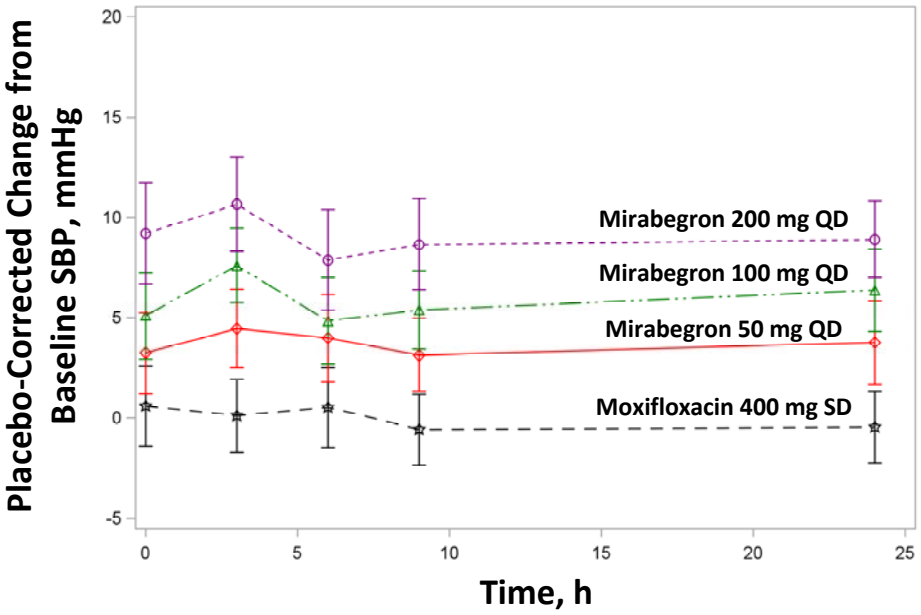


Figure 2: Dose dependent increase in SBP observed in the Study CL-178-077 at steady-state (Day 14). ***The error bars represent 95% confidence interval.***

It should be noted that moxifloxacin (active control for the QT part of the study) showed no change in blood pressure as expected. The maximum change in SBP with mirabegron 50 mg QD was 4.0 mmHg (1.64, 6.43). The 24-hour average effects are presented in the table below:

Treatment	24 hour average change in SBP, mmHg Mean (SD)
Moxifloxacin 400 mg QD	0.02 (11.2)
Mirabegron 50 mg QD	3.0 (10.2)
Mirabegorn 100 mg QD	5.5 (10.6)
Mirabegron 200 mg QD	9.7 (11.7)

Table 1: Summary of the 24 hour change in SBP at steady state in Study 178-CL-077

The effects of different treatment arms on SBP for the Phase III trials are discussed in detail in the Consult Review by Dr. Dunnmon, hence will not be discussed in detail in this document. The only additional point of interest is that in the pooled phase III data there is a consistent trend for increase in average SBP over 12-week trial durations for mirabegron 50 mg QD and mirabegron 100 mg QD treatment arms compared to placebo as shown in the Figure 3 below.

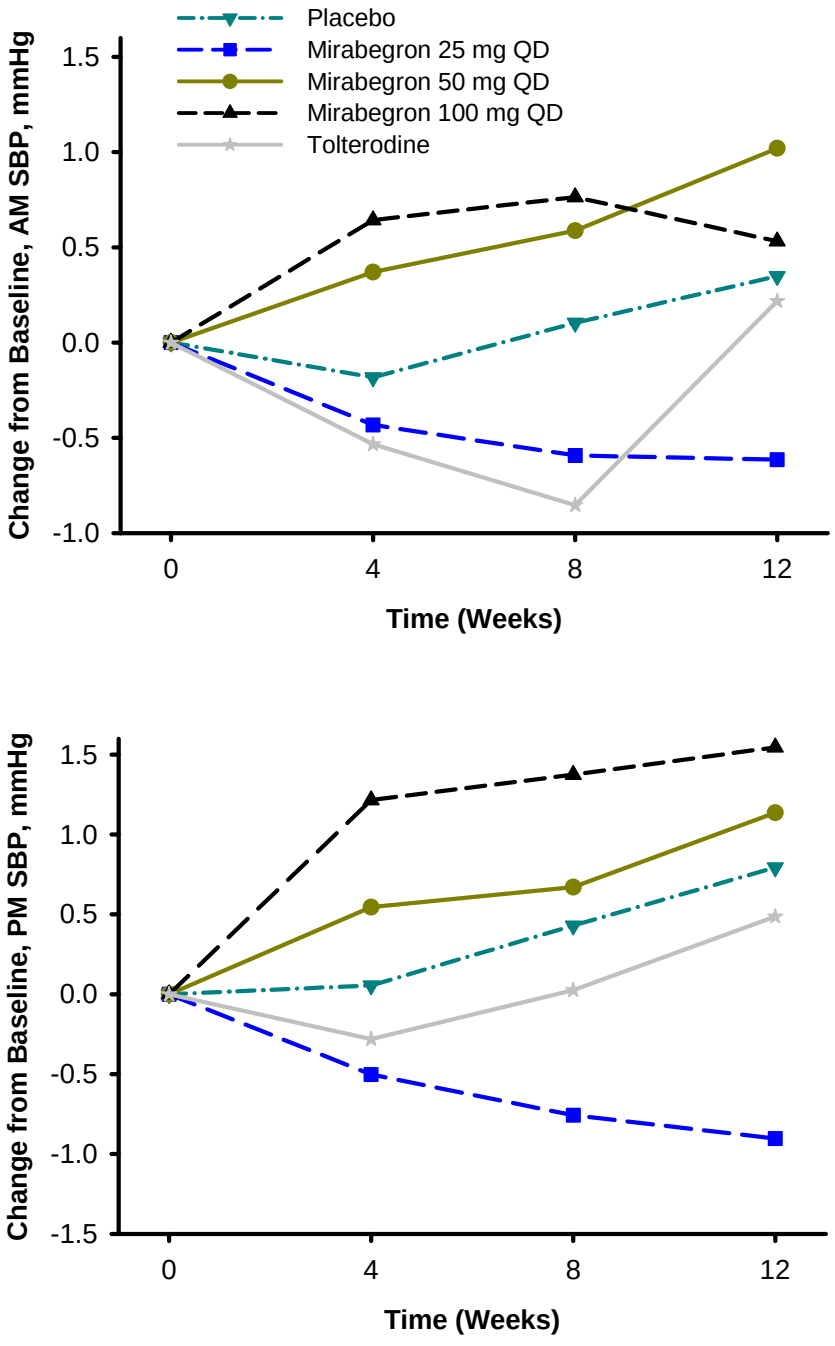


Figure 3: Time course for mean AM (above) and PM (below) SBP in phase III (pooled data from studies 178-CL-046, 178-CL-047 and 178-CL-074)

It should be noted that none of these differences are statistically significant compared to placebo and are lower than the effects observed in the TQT study. The potential reasons for under-estimating the blood pressure effects in phase III studies, as compared to what was demonstrated in the TQT study, are:

1) Use of different measurement techniques for blood pressure (self measurement in phase III versus office measurements in TQT study with time matched-baseline).

2) Timing of the blood pressure measurement. In TQT study, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at peak and trough. In the phase III studies, vital signs were collected by the subject during the AM (after waking up in the morning before the morning dose) and PM (between 2 PM and 6 PM) in a 5-day vital sign diary using a self-measurement device. This sampling scheme did not allow for the assessment of the peak effects which generally occurred around 3 – 4.5 hours coinciding with the peak mirabegron concentrations post-dose, as demonstrated by the histogram of post-dose timing of the afternoon blood pressure reading in the figure below.

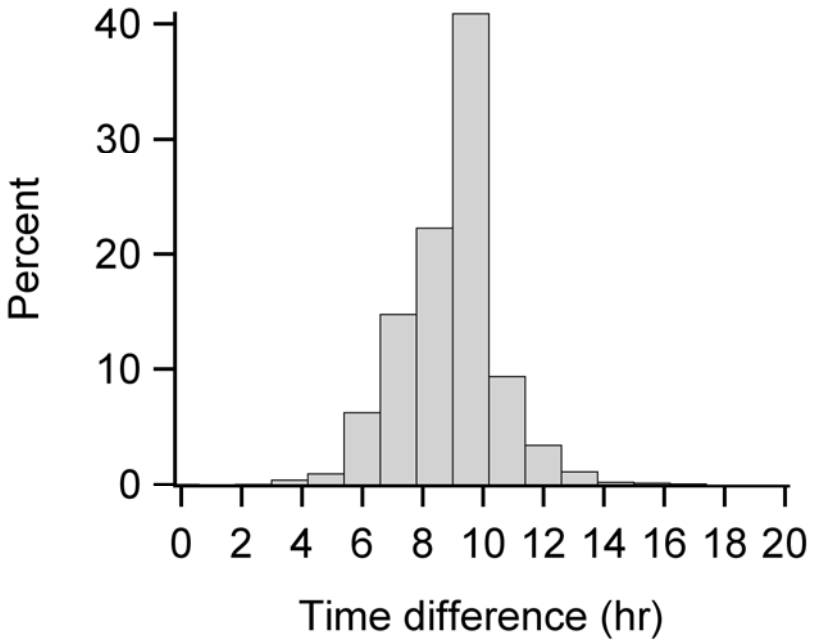


Figure 4: The peak effects are not assessed for most of the patients in the phase III trials at week 12. The time of the AM measurement is used as a reference for dosing time.

For the purpose of cardiovascular risk assessment in phase III, AM SBP (morning SBP obtained from the vital signs collected via Patient Diary) is utilized. This typically represents the trough SBP (SBP at the trough exposure of the treatment). For the treatment effect, the maximum AM SBP (the maximum of the three visits post-baseline derived from the ISS database; AVISIT = 7777) is considered. A brief

description of the derivation of the SBP measurement from the patient diary is provided in the Appendix.

The cumulative distribution of the change from baseline in morning SBP for the pooled Phase III trials (178-CL-046, 178-CL-047 and 178-CL-074) for Placebo and the mirabegron 50 mg QD, the dose for which approval is being sought is shown in the figure below. As expected based on the time-course, the cumulative distribution curve for mirabegron is shifted to the right by a small change in SBP of 0.5 mmHg (95%CI: -0.21, 1.16). These results suggest that SBP effect greater than 1.16 mm Hg can be ruled out with a certain confidence under the specific design used for blood pressure measurement in the Phase III trials.

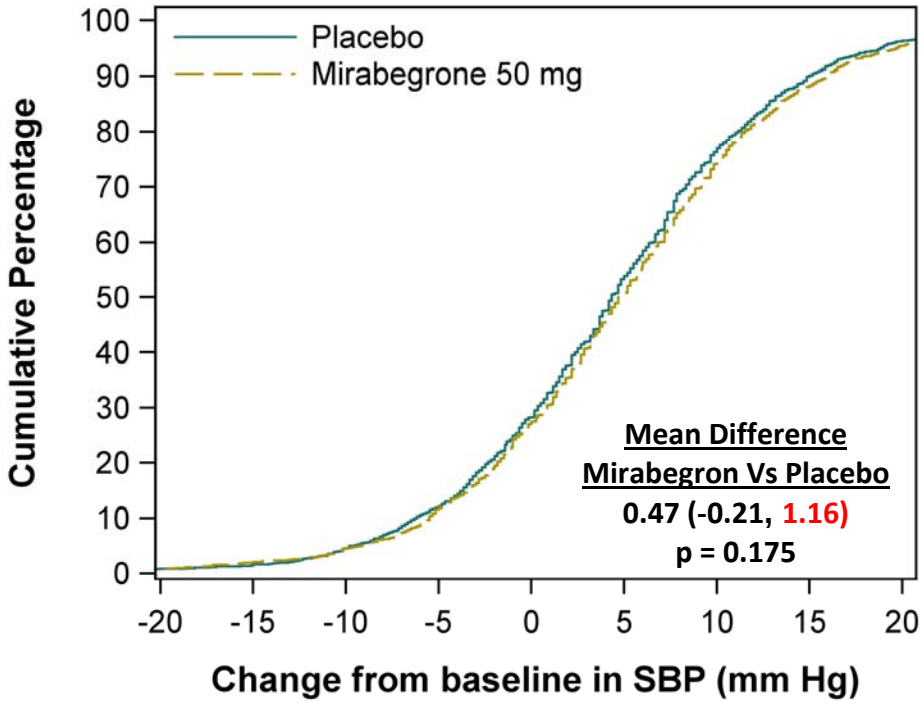


Figure 5: Cumulative distribution of maximum mean change from baseline AM SBP for the pooled phase III trials (178-CL-046, 178-CL-047 and 178-CL-074). ***The X-axis is truncated to -20 mmHg on the lower end and 20 mmHg on the higher end.***

2) What is the impact of change in SBP on the cardiovascular risk?

To assess the potential impact of the changes in SBP, the Cox-Proportional hazards model developed by D'Agostino et al was utilized[2]. This model provides a quantitative relationship between various risk factors and the probability of developing cardiovascular disease (CVD). CVD is defined as a composite of CHD

(coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral arterial disease (intermittent claudication), and heart failure. The various predictors of risk are sex, age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status. Using this model, 10-year general CVD risk can be assessed.

CVD risk assessment based on SBP effect observed in the 12-week phase III trials:

The change in 10-year general CVD risk was computed on the pooled Phase III data (178-CL-046, 178-CL-047 and 178-CL-074), taking into account various patient-specific risk factors and changes in AM SBP. The AM SBP typically represented the trough SBP during the trial. The SBP for the treatment effect was the maximum mean AM SBP observed post-baseline (explained on Page 4) obtained from the vital signs collected via Patient Diary. Patients receiving either systemic Beta Blockers or agents acting on Renin Angiotensin System (RAS) at baseline were flagged as receiving treatment for hypertension. The same definition was used for baseline and post-baseline visit. Patients with a history of diabetes at baseline were flagged for diabetes status.

In the Phase III trials, total cholesterol, high density lipoprotein, and smoking status were not collected. For the purpose of this analysis, the mean total cholesterol value and mean HDL cholesterol value by age and gender based on the National Health and Nutrition Examination Surveys (NHANES) [Carroll et al, 2005[4]] was used for each patient. Patients between the ages of 18 and 19 years are not covered by NHANES, so they were assigned the mean total cholesterol value and mean HDL cholesterol value for the age group of 20 to 29 years by gender based on NHANES. Smoking status was based on the age- and gender-specific average percentage of current cigarette smokers in 2010 for the United States from the National Health Interview Survey (NHIS)[5]. These imputations were proposed by the sponsor and accepted by the Agency.

The change in 10-year general CVD risk was also computed for patients with high baseline risk. High risk patients were defined as those patients in the upper 25% of the baseline risk. For the pooled Phase III studies this comprised patients with a 10-year CVD risk greater than 19.9%.

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[4] *Carroll etal. Trends in serum lipids and lipoproteins of adults, 1960-2002. JAMA. 2005;294(4):1773-81.*

[5] *Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥ 18 years --- United States 2005 – 2010. MMWR. 2011;60(35):1207-12.*

A summary of the available baseline risk factors for the pooled phase III trials is presented in the Table 2 below.

Patient Characteristics	Placebo N = 1329	Mirabegron 50 mg N = 1327
Age, yrs (Mean, [SD])	59 (13)	60 (13)
SBP, mmHg (Mean, [SD])	126 (17)	126 (17)
Gender, M/F	363/966	383/944
Antihypertensive Treatment, %	40	39
Diabetes Status, %	8.0	9.0

Table 2: Summary of the available baseline risk factors for assessment of 10-year general CVD risk by treatment for the pooled phase III trials

The small increases in SBP for the pooled twelve-week phase III trials translate into a small increase in the 10–year general CVD risk a shown in Figure 6 below. The absolute increase in the mean 10-year CVD risk on an average is 0.19% (or 0.19 CVD events per 1000 patient-years) and fails to achieve statistical significance.

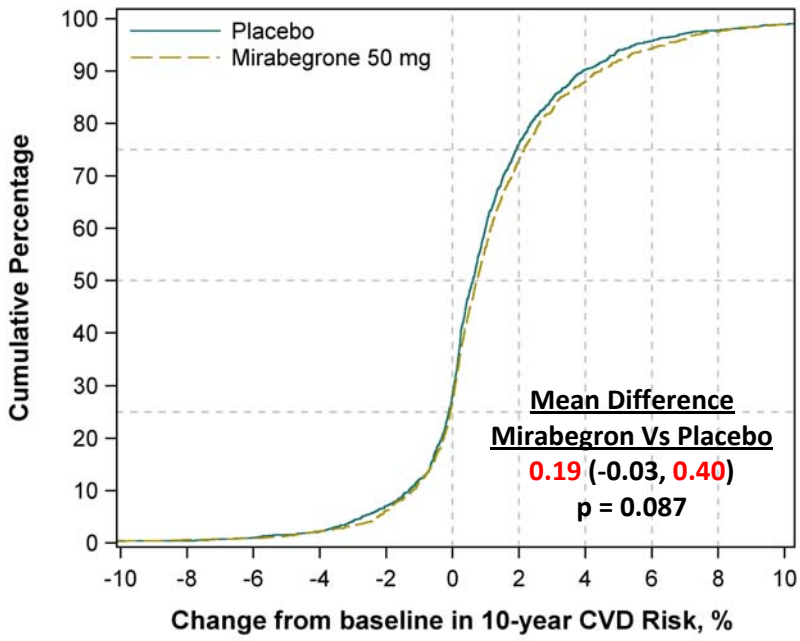

Figure 6: Cumulative distribution plots for change from baseline in 10-year general CVD risk for Placebo and Mirabegron 50 mg QD based on the SBP effects observed in the twelve-week phase III trials

The prevalence of OAB is estimated to be 34 million in the United States[6]. When this increase in the CVD risk of 0.19 events/1000 patient-years is extended to an OAB population (with risk characteristics similar to those in the phase III studies) of a million patients on treatment with mirabegron 50 mg QD for 1 year, 187 additional CVD events projected, per the figure below.

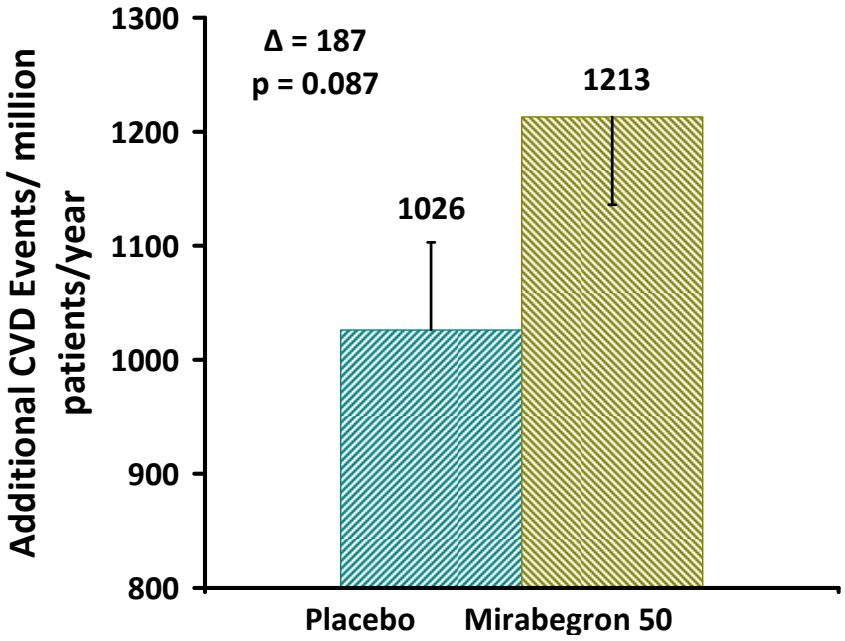

Figure 7: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the SBP effects observed in the twelve-week phase III trials

This increase in the CVD risk is magnified in patients with a higher baseline risk (patients in the upper 25th percentile of baseline CVD risk) as shown in the Figures 8 & 9 below. These patients in general tend to demonstrate more advanced age (median: 70 years), higher baseline AM SBP (median: 141 mmHg), a greater proportion of diabetes (22 – 23%), more treatment for hypertension (67 – 68%) and higher baseline 10-year CVD risk (median: 30.6%). Accordingly, in these higher risk patients on treatment with mirabegron 50 mg QD for 1 year, an additional 556 CVD events are projected per million patients (still not statistically significant, p-value derived based on 25% of the total sample size in the Phase III trials).

[6] *Irwin etal. Understanding the elements of overactive bladder: questions raised by the EPIC study. BJU Int. 2008;101:1381–1387*

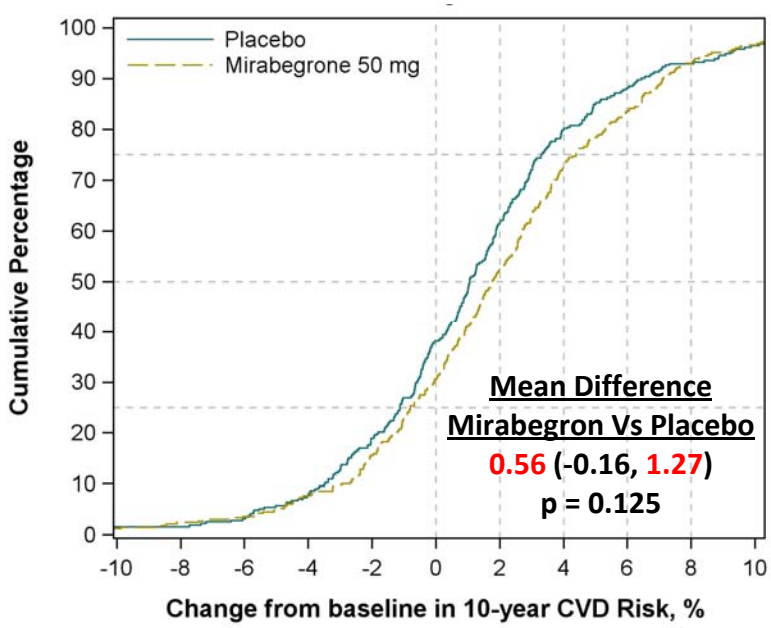

Figure 8: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD in high risk patients based on the SBP effects observed in the twelve-week phase III trials

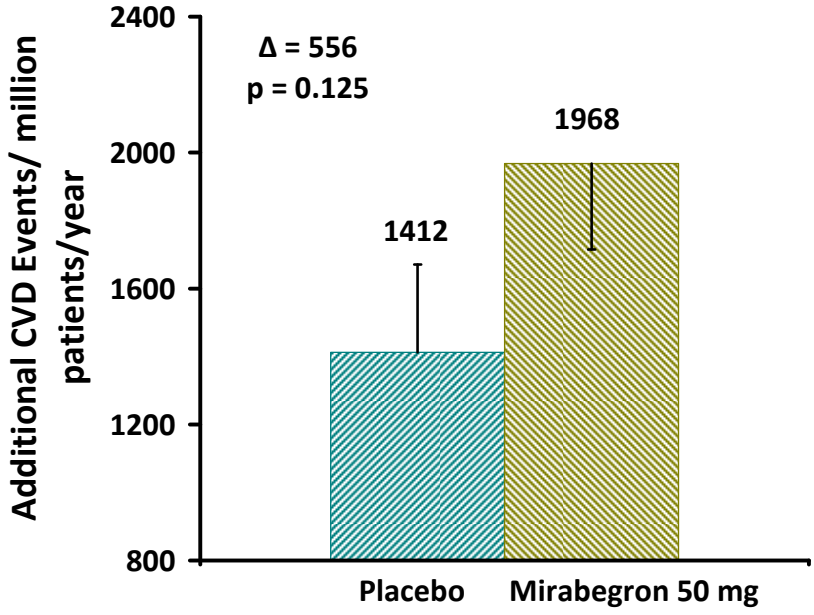

Figure 9: Projection of the cardiovascular impact of the increase in 10-year CVD risk for placebo and mirabegron in high risk patients based on the SBP effects observed in the twelve-week phase III trials

CVD risk assessment based on SBP effect observed in the TQT Study:

The blood pressure effects observed in the TQT study represent a relatively precise estimate of the blood pressure effects of mirabegron as these results were obtained under tightly controlled conditions. It is not unreasonable to assume that the effects observed in this study are representative of the true SBP effects of mirabegron. The design and conduct of phase III trials generally do not allow detection of peak or mean effects. The analysis presented below represents an effort to understand the potential cardiovascular impact of the blood pressure effects observed in the TQT study.

Blood pressure effects associated with the treatment of placebo and mirabegron 50 mg QD were simulated based on the results presented in the Table 1 assuming normal distributions. The 24-hour average (corrected for placebo and baseline) change in blood pressures represented the change from the baseline AM SBP (i.e., trough) for the pooled phase III data. The effect observed for the moxifloxacin arm in the TQT study (Mean [SD]: 0.02 mmHg [11.2]) was used to simulate the placebo effect for the placebo arm (N =1329) while that observed for mirabegron 50 mg QD (Mean [SD]: 3.0 [10.2]) was used for the mirabegron arm (N = 1327) for the pooled phase III trial data. All the other risk factors at baseline and end or treatment were retained from the observed phase III data.

The projection of the change in the 10-year CVD risk and its impact per-million patient-years are presented in the Figures below for the overall population (Figures 10 and 11) and patients with high baseline risk (Figures 12 and 13).

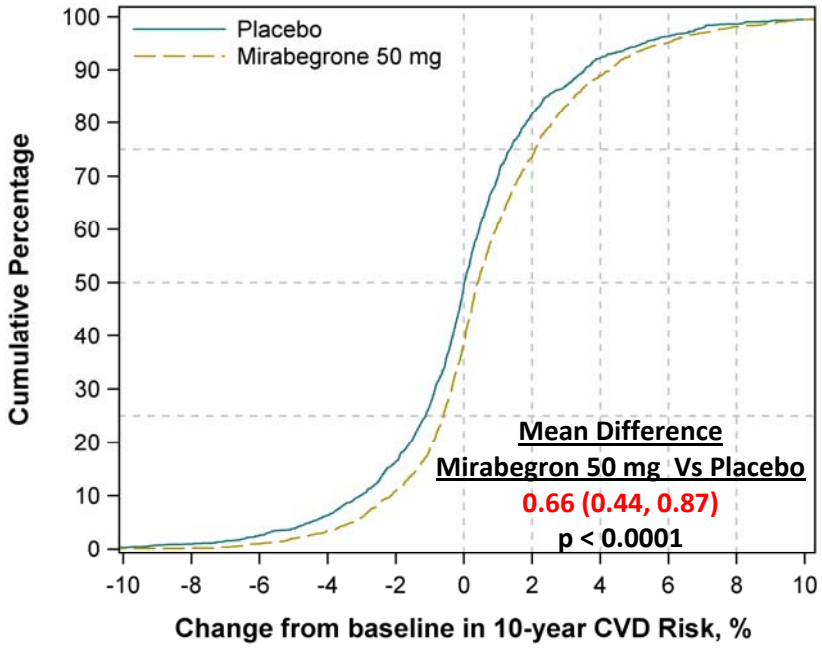

Figure 10: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD based on the simulated blood pressure effects derived from TQT study

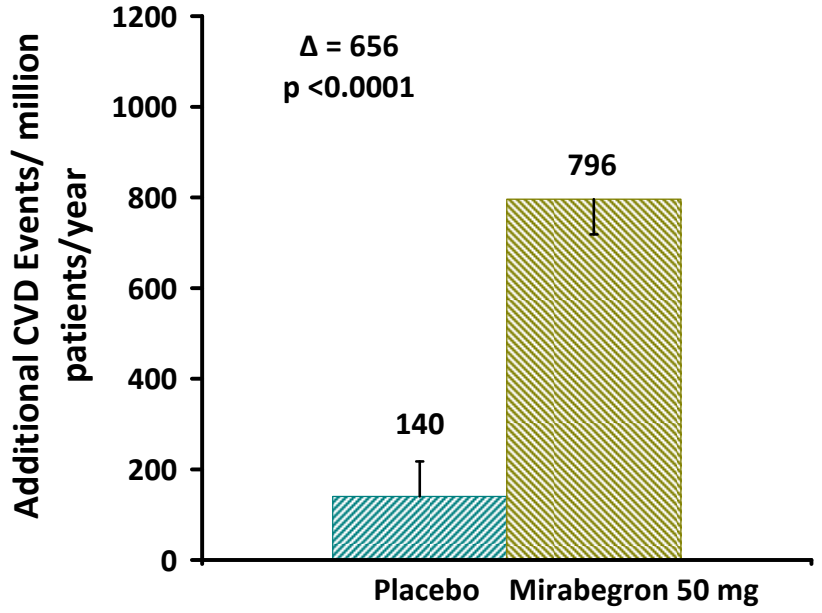

Figure 11: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the simulated blood pressure effects derived from TQT study

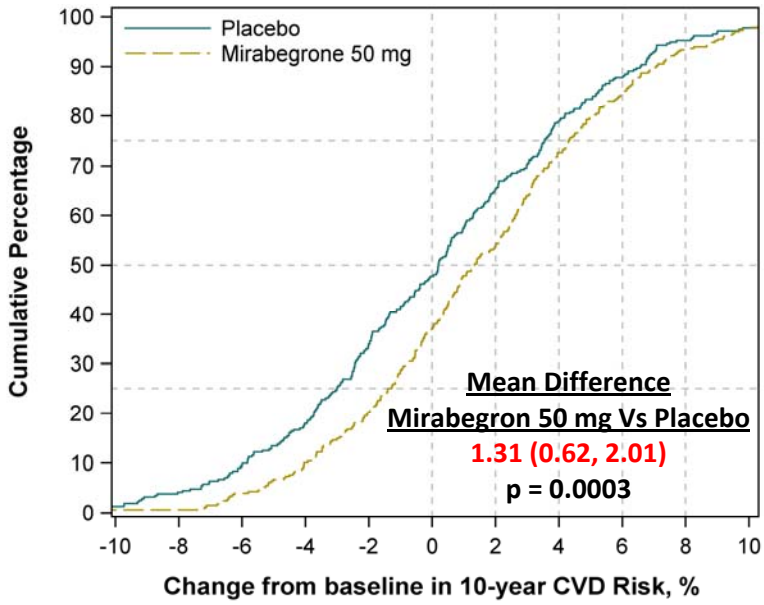

Figure 12: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD based on the simulated blood pressure effects derived from TQT study in high risk patients

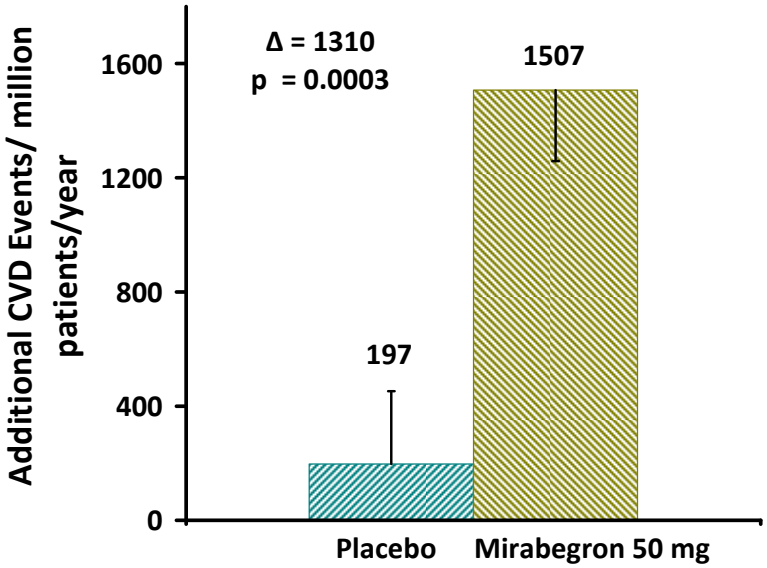

Figure 13: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the simulated blood pressure effects derived from TQT study in high risk patients

As would be expected, the higher demonstrated blood pressure elevation in the TQT study predicts a higher risk of CVD events than did the phase III data.

Appendix:

The following is a brief description of the systolic blood pressure collection and the calculation of the average excerpted from sponsor's Integrated Summary of Safety.

"**Vital Sign Conventions**
The vital sign collection method and conventions described below are applicable to the EU/NA OAB 12-week Phase 3 and EU/NA Long-term Controlled populations.
Vital sign measurements (systolic and diastolic blood pressure and pulse rate) are collected in two ways. For the ISS, diary measurements will be used for all analyses of vital signs. Each subject records vital sign measurements in a 5-day diary period preceding the study visit (e.g., for the 12-week studies: Randomization Visit, Week 4, Week 8, Week 12, and Final Visit) using a self-measurement device. For each diary day, the subject will collect AM measurements (after waking in the morning but prior to breakfast and double-blind study drug intake) and PM measurements (between 2 pm and 6 pm in the afternoon). Subjects are to take 3 readings which are approximately 2 minutes apart for both the AM and PM measurements.

Averaging Vital Signs Measurement
Diary Measurement
An average will be calculated for AM and PM measurements separately for each vital sign variable (SBP, DBP and pulse rate). The average for each day will first be calculated and then the average over the diary days will be calculated.
The last 2 vital sign values measured each day for AM and PM with the subject's self-measurement device will be utilized for the AM and PM analyses. If only 1 or 2 measurements are taken in the AM or PM, then all values will be utilized in the AM or PM analyses.
If a subject recorded a vital sign measurement for ≥ 4 diary days for AM or PM, an average will be calculated based on the last 3 diary days provided they are within the analysis window for a given visit. If a vital sign measurement is recorded for only 1 to 3 diary days, an average will be calculated based on all diary days within the analysis window for a given visit."

REVIEW OF NEOPLASMS:

Division of Oncology Products

E

Consultation Request and Specific Questions

The original Request for Consultation from the Division of Reproductive and Urologic Products has the following background information and questions:

"NDA 202611, mirabegron, is a new marketing application indicated for overactive bladder. Mirabegron is a new molecular entity, first in its class (beta-3 adrenoceptor agonist) with a PDUFA Goal date of June 29, 2012. The submission is fully electronic and is located at this site: \\CDSESUB1\EVSPROD\NDA202611\202611.enx

The application is scheduled for an Advisory Committee (AC) Meeting on April 5, 2012. We are respectfully requesting your Division to review the application in regard to adverse event reports of a variety of solid tumors (benign and malignant neoplasms). Most, but not all, of the AE reports of neoplasms occurred during the 1 year, active-controlled Study 049, with an apparent excess in the mirabegron 100 mg arm compared to both the mirabegron 50 mg arm and the tolterodine arm. At this time, we are planning to present the adverse event reports of neoplasms as a issue to the AC. Our main concern lies in the inbalance between groups in Study 049. We have less concern regarding neoplasms that were reported as AEs in the short-term (12-week) pivotal studies. We seek your input as we prepare for the AC meeting. We have the following specific questions:

1. *In your opinion, are the results of Study 178-CL-049 (Study 049) for the number of neoplasms accurately stated in the study report?*

2. *Do you agree with the Adjudication Committee's case-by-case analysis of neoplasms in Study 049? In your opinion, can any of the cases of neoplasms reported in Study 049 be excluded? If so, what is the reason for exclusion?*

3. *The number of neoplasms reported was greater in the mirabegron 100 mg group compared to the mirabegron 50 mg group in Study 049. Are you aware of any similar situation, in which the incidence of neoplasms was found responsive to a 2-fold increase in dose, such as is observed in Study 049? If not, in your opinion, would it be appropriate to pool the data from the mirabegron 50 mg and 100 mg groups to analyze the neoplasms reported in Study 049?*

4. *In your opinion, how should the neoplasm data from Study 049 be analyzed? In your response, please consider whether to include previous exposure to mirabegron, tolterodine, or placebo in studies that took place prior to Study 049.*

5. *Neoplasms were also reported in short-term (≤ 12-week) studies. Most of the neoplasms in patients taking mirabegron (7/8) in short-term studies were reported in Study 047. In your opinion, should neoplasms reported in short-term studies be included in the FDA's overall analysis of neoplasms?*

6. *Are there any other analyses that you suggest be conducted, such as pharmacokinetic/pharmacodynamic (PK/PD) analyses, Kaplan-Meier analyses, or relative risk analysis?*

DOP1 Responses

Background:

Mirabegron is a beta 3-adrenoceptor agonist that represents a new molecular entity. In NDA 202611, the product is proposed for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. The recommended dosing schedule for the proposed indication of mirabegron is 50 mg administered orally once daily.

To support this NDA, the applicant submitted 5 randomized, double-blind, placebo- and/or tolterodine-controlled Phase 3 trials in the intended patient population. Tolterodine was used as an active control in some of the trials. These trials are listed in **Appendix 1**. Four of the five trials, including Studies 178-CL-046, 178-CL-047, 178-CL-048, and 178-CL-074, had a 12-week double-blind treatment period; whereas one of the five, Study 178-CL-049, had a 12-month treatment period, designed to examine the long-term safety of mirabegron. For simplicity, all the studies discussed below are hereafter referred by the last three numbers of study identifiers.

For this consultation, the DRUP review is more concerned about the imbalance in the neoplasms detected among groups in Study 049. This study was conducted between April 25, 2008 and May 6, 2010, with a total of 2452 patients enrolled. Of them, 2444 patients were included for safety evaluation. The following table summarizes the neoplasms reported as an SAE from this study by the applicant. The detailed summary regarding the timing of diagnoses and the applicant's assessment of malignancy attribution to study agent is listed in **Appendix 2**. It is noted that approximately 80% of patients in Study 049 had been previously enrolled in Studies 046 or 047.

Number of Serious Neoplasms (Benign and Malignant) Reported in Study 049

	Tolterodine ER 4 mg (n=812)	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)
Benign	2*		1
Malignant			
Breast Cancer	2		2
Endometrial Cancer	1	1	1
Urothelial Carcinoma			1
Prostate Cancer			2
Lung Cancer			2
Thyroid Tumor**			1
Pancreatic Carcinoma			1
Total # of Malignant Tumors	**3**	**1**	**10**

*One patient (ID 3020-0298) had a hamartochondroma in the right lung in addition to the diagnosis of breast cancer

** Not fully determined since the cold nodules in the left lobe was not removed. Malignancy could not be ruled out in this case.

Response to Question 1*: In your opinion, are the results of Study 178-CL-049 (Study 049) for the number of neoplasms accurately stated in the study report?*

Based on the 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.

Additional neoplasms reported as non-SAE, treatment emergent adverse event (TEAE) were found in the dataset and are listed in the following table by treatment arm. The majority of these non-SAE neoplasms were benign. The malignant neoplasms appear to be skin-associated. These additional neoplasms were included in the tabulation of TEAEs in Table 12.6.1.4 of the Applicant's study report.

	Tolterodine ER 4 mg (n=812)	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)
Benign	ID: 178-CL-047-U00015976695 (pulmonary nodules*) ID: 178-CL-049-1656-0578 (fibroadenoma, intraductal papilloma) ID: 178-CL-049-2203-0642 (Uterine Fibroid)	ID: 178-CL-046-3028-1680 (tumor in the right breast (benign) ID: 178-CL-047-U00008727873 (Wart on fourth finger) ID: 178-CL-047-U00020386712 (neuroma left foot) ID: 178-CL-047-U00021796744 (Uterine Fibroids	ID: 178-CL-046-3132-2915 (basalioma cutis) ID: 178-CL-047-U00016048278 (Benign Breast Lump)
Malignant	ID: 178-CL-047-U00016436933** (cutaneous SQUAMOUS CELL CA)	ID: 178-CL-046-3232-1066 (Malignant nasal basalioma ID: 178-CL-047-U00019417928(basal cell carcinoma, numerous sites) ID: 178-CL-049-1608-0503 (basal cell carcinoma)	ID: 178-CL-047-U00016427000 (basal cell carcinoma) ID: 178-CL-047-U00018387657 (basal cell-superior helix)
* Several small nodules of 1-4 mm scattered in the lungs, with one nodule disappeared and an additional one decreased in size in follow-up CT scan. Diagnosed of benign lung nodules clinically. **Patient 00016436933 was an 80 year-old man who had a history of cuSCC			

Response to Question 2: *Do you agree with the Adjudication Committee's case-by-case analysis of neoplasms in Study 049? In your opinion, can any of the cases of neoplasms reported in Study 049 be excluded? If so, what is the reason for exclusion?*

Yes. The submitted narratives show that all the serious neoplasms, except for Case 3016-1796 (fibroma), were supported by pathological evidence and cannot be excluded.

Response to Question 3: *The number of neoplasms reported was greater in the mirabegron 100 mg group compared to the mirabegron 50 mg group in Study 049. Are you aware of any similar situation, in which the incidence of neoplasms was found responsive to a 2-fold increase in dose, such as is observed in Study 049? If not, in your opinion, would it be appropriate to pool the data from the*

mirabegron 50 mg and 100 mg groups to analyze the neoplasms reported in Study 049?

Not to the consultant's best knowledge. In addition, the consultant noted that the recommended dose for the proposed indication is 50 mg once daily. The investigational dose of mirabegron 100 mg once daily that was used in clinical trials is not recommended in the draft product label. The increased number of neoplasms in the mirabegron 100 mg group is of 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:

A) **The detected neoplasms were heterogeneous in tissue of origin.**

B) **Appendix 2 shows that 5 of the 11 neoplasm SAEs in the mirabegron 100 mg group were diagnosed within 12 weeks of study treatment and that 2 of the 11 diagnosed between Months 3-6 of treatment initiation.**

The remaining 4 cases, including the above case of fibroma, were found between months 6-12 of the trial. This is comparable to the time course of the 3 neoplasms found in the tolterone control arm.

C) The consultant did not find a remarkable imbalance in the incidence of malignancies among the four 12-week Phase 3 trials of the product. However in the 1-year study, 5 of the 11 cases occurred within the first 12 weeks as stated above.

Response to Question 4: *In your opinion, how should the neoplasm data from Study 049 be analyzed? In your response, please consider whether to include previous exposure to mirabegron, tolterodine, or placebo in studies that took place prior to Study 049.*

Please see Response to Question 3.

The significance of previous exposure to mirabegron, tolterodine, or placebo is difficult to estimate. There is no apparent relationship between prior exposure and neoplasm detection in Study 049, as suggested in Appendix 2, Table 24, below.

Response to Question 5: *Neoplasms were also reported in short-term (≤ 12-week) studies. Most of the neoplasms in patients taking mirabegron (7/8) in short-term studies were reported in Study 047. In your opinion, should neoplasms reported in short-term studies be included in the FDA's overall analysis of neoplasms?*

Given that there were four randomized, 12-week Phase 3 trials of mirabegron 50 mg in comparison with placebo and/or tolterodine, you may conduct a pooled analysis of neoplasms across the four trials to evaluate whether treatment with mirabegron 50 mg for 12 weeks was associated with an increased diagnosis of neoplasms.

The consultant noted that Study 047 had 442 patients treated with mirabegron 50 mg once daily, representing approximately 25% of the total patients (1754) who received 50 mg mirabegron once daily in the four randomized, short-term trials.

Response to Question 6: *Are there any other analyses that you suggest be conducted, such as pharmacokinetic/pharmacodynamic (PK/PD) analyses, Kaplan-Meier analyses, or relative risk analysis?*

No additional recommendations with regard to the reported imbalance in neoplasms in Study 049. You may want to discuss the need for further studies at your upcoming Advisory Committee meeting.

Please also see Response to Question 3 above.

Appendix 1*:* Key Studies in Support of the NDA 202611 for Mirabegron

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies *continued*								
E/S	178-CL-046 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 Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	1987†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-047 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 Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food	1329†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-048 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 Mirabegron OCAS 50 mg tablet or matching placebo po; once daily with food (after breakfast) tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with food (after breakfast)	1139†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-074 Canada, Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden, 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 Mirabegron OCAS 25 or 50 mg tablet or matching placebo po; once daily with or without food	1306†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-049 Europe§ Canada United States Australia New Zealand South Africa	Long term safety	Phase 3, randomized, double-blind, active-controlled	Treatment groups: Mirabegron 50 or 100 mg, or tolterodine ER mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine ER 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	2452†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12 month double-blind treatment period	Complete; Full

Appendix 2: (Adopted from Pages 120-121 of Study Report for Study 178-CL-049)

Table 24 Serious Treatment-emergent Adverse Events of Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) (SOC)

Patient No. Age/Race/Sex	MedDRA (v9.1) Preferred Term (Reported Term)	Onset/ Stop Day (Last Dose Day)	Severity/ Outcome	Relationship to Study Drug	Treatment in Previous Study (046/047/ Naive)
Mirabegron 50 mg					
2179-6744 54/White/Female	Endometrial cancer stage I (endometrial grade 1 cancer)	315/350 (364)	Mild/ Recovered	Not Related	placebo (047)
Mirabegron 100 mg					
1597-7875 61/White/Female	Breast cancer (left breast cancer)	86/ ongoing (294)	Moderate/ Recovering	Not Related	mirabegron 100 mg (047)
1651-8100 70/White/Male†	Prostate cancer (prostate cancer)	54/ ongoing (58)	Severe/ Not Recovered	Not Related	mirabegron 50 mg (047)
2262-0172 52/White/Female†	Endometrial cancer (endometrioid cancer)	139/216 (166)	Mild/ Recovered	Not Related	naive
3016-1796 48/White/Female	Fibroma (hypopharynx fibroma)	329/332 (364)	Moderate/ Recovered	Not Related	tolterodine SR 4 mg (046)
3016-1952 61/White/Female†	Lung neoplasm malignant (lung ca)	126/ ongoing (175)	Severe/ Not Recovered	Not Related	mirabegron 50 mg (046)
3022-0128 69/White/Male†	Prostate cancer (prostate carcinoma)	49/85 (82)	Severe/ Recovered	Not Related	naive
3025-2505 64/White/Male†	Pancreatic carcinoma (carcinoma of head of the pancreas)	323/376 (323)	Severe/ Unknown	Not Related	tolterodine SR 4 mg (046)
3032-2166 69/White/Male	Thyroid neoplasm (recurrent tumor with cold nodule)	263/269 (364)	Moderate/ Recovered	Not Related	mirabegron 100 mg (046)
3034-2276 71/White/Female	Breast cancer (Carcinoma of mamma right)	92 E/ (362)	Moderate/ Not Recovered	Not Related	placebo (046)
3062-2853 58/White/Male†	Transitional cell carcinoma (urothelial carcinoma)	309/ ongoing (308)	Severe/ Not Recovered	Not Related	placebo (046)
3235-2623 74/White/Female†	Lung neoplasm malignant (pulmonary cancer)	53/ ongoing (55)	Severe/ Not Recovered	Not Related	placebo (046)
Tolterodine ER 4 mg					
3013-0077 51/White/Female	Breast cancer (mamma carcinoma right side)	203/ ongoing (370)	Moderate/ Unknown	Not Related	naive
3020-0298 60/White/Female	Benign lung neoplasm (hamartochon-droma right lung)	300/353 (364)	Moderate/ Recovered	Not Related	naive
	Breast cancer (mamma carcinoma right)	293/ ongoing (364)	Moderate/ Not Recovered	Not Related	
3068-3245 40/White/Female	Uterine leiomyoma (uterus polymyomia)	85/149 (363)	Moderate/ Recovered	Not Related	tolterodine SR 4 mg (046)
3235-1509 64/White/Female†	Endometrial cancer (endometrial cancer)	296/ ongoing (317)	Severe/ Not Recovered	Not Related	tolterodine SR 4 mg (046)

Addendum to Memorandum of Consultation

Division of Oncology Products 1 (DOP 1)
Office of Hematology and Oncology Products (OHOP)

This addendum was generated to address an additional concern about the potential risk of increased neoplasms in the 50 mg mirabegron arm.

After evaluating relevant information in the original consult and the label of tolterodine, the control product used in the Study 178-CL-049, the consultants agreed to add the following to the previous responses:

While a signal was not evident in the mirabegron 50 mg cohort, given the study size, the consultants cannot rule out an increased risk for the development and or detection of neoplasm.