CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	June 26, 2012
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA#	202,611
Applicant	Astellas Pharma Global Development, Inc.
Date of Submission	August 29, 2011
PDUFA Goal Date	June 29, 2012
Proprietary Name / Established (USAN) names	MYRBETRIQ mirabegron
Dosage forms / Strength	25 mg and 50 mg extended-release tablets
Proposed Indication(s)	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency
Recommended:	***Approval***

1. Introduction

The symptoms of overactive bladder (OAB) are urinary frequency, urinary urgency (the need to urinate immediately), and urge urinary incontinence. Epidemiology studies show that OAB affects roughly 12-16% of adults. Patients with OAB, especially those with urge incontinence, are often prevented from fully engaging in activities of daily life, and may miss out on important events. OAB patients with urgency and frequency often prepare for daily activities by learning the available toileting facilities, limiting fluids, and restricting travel plans. For patients with "wet" OAB, there is the additional burden of hygiene and emotional disturbances, such as shame and embarrassment.

Currently, the armamentarium available to clinicians for the treatment of OAB is very limited. Non-invasive therapies include limiting fluids (especially diuretics), timed voiding schedules, and behavioral therapy, such as biofeedback. There are also more invasive methods, such as peripheral nerve stimulation.

The mainstay of treatment for OAB is anti-muscarinic medication. Most anti-muscarinic medications for OAB are administered orally, but there are also topical gels and topical transdermal systems. The oral medications currently available include oxybuynin (Ditropan, Ditropan XL), tolterodine (Detrol, Detrol LA), feosterodine (Toviaz), trospium chloride (Sanctura and Sanctura XR), solifenacin (VESIcare) and darifenacin (Enablex). The topical formulations of oxybutynin include the Oxytrol patch and Gelnique gel. All these medications act by antagonizing muscarinic receptors in the bladder (detrusor) smooth muscle, thereby inhibiting involuntary detrusor muscle contractions which lead to the symptoms of OAB. These medications also serve to increase bladder capacity modestly during the filling phase of the voiding cycle. The success of anti-muscarinic therapy for OAB is limited by its modest treatment effect and by anti-muscarinic side effects, especially dry mouth, constipation, and urinary retention.

Mirabegron is a beta-3 adrenergic agonist for the treatment of OAB. Studies have demonstrated that the activation of beta-3 adrenergic receptors residing on the bladder (detrusor) smooth muscle serves to inhibit involuntary detrusor muscle contractions and

modestly increase bladder capacity. Thus, mirabegron presents an opportunity to exploit a different physiologic mechanism for the improvement of OAB symptoms and the side effect profile is different from the traditional anti-muscarinic therapy.

Astellas Pharma Global Development has conducted an extensive and robust development program for mirabegron for the treatment of OAB, including three, EU/NA, randomized, double-blind, placebo-controlled, 12-week, efficacy and safety (Phase 3) studies (Studies 178-CL-046, -047, and -074), as well as a randomized, double-blind, double-dummy, 52-week, active-controlled, long-term safety study (178-CL-049). Astellas also conducted a number of Phase 2 studies, as well as a host of Phase 1, safety, tolerability, PK and drug interaction studies.

2. Background

2.1 DESCRIPTION OF PRODUCT

Mirabegron is a beta-3 adrenergic agonist. Mirabegron is intended to alleviate overactive bladder symptoms by agonist activation of beta-3 adrenoceptors in the bladder wall, resulting in relaxation of the bladder detrusor muscle. Increased bladder capacity and reduced bladder contractions with mirabegron were reported in animals. In vitro data suggest that mirabegron is primarily a beta-3 adrenergic agonist with minimal beta-1 and little beta-2 adrenergic activity in animals or in humans. However, animal studies and a clinical study suggested that mirabegron has potential for off-target activation of beta-1 adrenoceptors, which at supratherapeutic doses has resulted in increased heart rate and blood pressure.

Mirabegron will be supplied as oval, extended-release, brown or yellow, film-coated tablets in the dose strengths of 25 mg or 50 mg. The extended-release tablet utilizes an Oral Controlled Absorption System (OCAS) system developed by Astellas Pharma. The tablets are to be taken once daily with water. The main components of the product are the drug substance. polyethylene oxide (b) (4) and polyethylene glycol (b) (4) (PEG). (b) (4) .

2.2 REGULATORY HISTORY

On December 21, 2005, a Pre-IND meeting was held. The Division expressed concerns regarding increases in heart rate and blood pressure observed in patients at 160 mg (IR formulation), as well as increases in serum transaminases observed in several patients, among other issues.

On May 9, 2006, new IND #69,416 was submitted. The opening clinical protocol was a drug interaction study with ketoconazole, a strong inhibitor of CYP3A4.

On November 14, 2007, an End-of-Phase 2 (EOP2) meeting was held, at which time the planned Phase 3 studies were discussed. Several safety issues were discussed, including isolated cases of elevations in liver function tests, and increases in blood pressure in some individuals in Phase 2 studies. The Division requested that blood pressure and liver function be monitored in the Phase 3 studies.

In January, 2008, the Phase 3 study protocols were submitted for special protocol assessments (SPA). The Division recommended that in addition to the 50 mg and 100 mg dose being studies, a 25 mg dose of mirabegron be evaluated. (b) (4)

In March – August, 2010, the Division held three teleconferences with Sponsor to discuss mirabegron and adverse events of "glaucoma" reported during the mirabegron development program. After review of additional analyses and data, the Division remained concerned that mirabegron could increase intra-ocular pressure (IOP). The Sponsor proposed to conduct a study to evaluate the direct effect of mirabegron on IOP. That proposal was reviewed by the Division of Transplant and Opthalmologic Drug Products (DTOP). The study protocol for the IOP study (178-CL-081) was submitted on September 22, 2010.

On November 2, 2010, a Pre-NDA meeting was held. The preliminary Phase 3 study results were discussed. The Sponsor stated that they would systematically review several adverse events of interest, to which the Division agreed. The AEs of interest were:

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

On August 29, 2011, original NDA 202,611 was submitted for mirabegron.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Roger Wiederhorn, stated in his final review, dated June 1, 2012:

> *"Recommendation on Regulatory Action: It is recommended that NDA 202-611 be **APPROVED** at this time.*
>
> *Risk Benefit Assessment: A thorough and comprehensive review of NDA 202-611 was carried out.* ***The NDA submission provided substantial evidence from adequate and well controlled ("pivotal") studies that mirabegron 25 mg and 50 mg is safe and effective for the treatment of overactive bladder.***
>
> *Efficacy data from three, Phase 3 studies (178-CL-046, -047, and -074) demonstrates that the primary efficacy objectives (reduction in daily incontinence episode and micturition frequency) were achieved in all three studies for mirabegron 50 mg once daily, as well as in Study 178-CL-*

074 for mirabegron 25 mg daily. While the primary efficacy endpoint data were comparable between mirabegron 25 mg and mirabegron 50 mg in Study 178-CL-074, a modest benefit of the 50 mg dose over the 25 mg dose was observed for several clinically meaningful secondary efficacy endpoints. In order to maximize the risk/benefit equation for mirabegron, this reviewer considers it reasonable and appropriate to initiate mirabegron therapy at 25 mg once daily, to provide a trial of the 25 mg dose, and to increase the dose to mirabegron 50 mg daily on an individual patient basis as needed, based on efficacy and tolerability of the 25 mg dose. The drug product labeling will recommend such dosage and administration.

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

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

There were no deaths attributable to mirabegron in the development. In regard to SAEs, there were no differences observed in incidences between total mirabegron and placebo. The only serious adverse event reported by more than 1 mirabegron patient and at a rate greater than placebo was atrial fibrillation (mirabegron 50 mg, 0.2%). Adverse events leading to study discontinuation were only modestly higher in incidence for the total mirabegron group (3.8%) compared to placebo (3.3%), and the mirabegron incidence was lower than the incidence reported for the active comparator (4.4%).

The most common TEAE (by PT) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 6/2736 [0.2%]; placebo: 3/1380 [0.2%]; tolterodine: 1/495 [0.2%]), headache (mirabegron: 6/2736 [0.2%]; placebo: 5/1380 [0.4%]; tolterodine: 2/495 [0.4%]) and hypertension (mirabegron: 6/2736 [0.2%]; placebo: 2/1380 [0.1%]; tolterodine: 1/495 [0.2%]).

For the mirabegron 50 mg dose, the most frequent adverse reactions leading to discontinuation in the Phase 3, 12-Week, OAB studies were hypertension (0.2%) and tachycardia (0.1%).

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

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

- *Mirabegron was associated with a modest increase in heart rate and blood pressure in Phase 3 studies. Mean increase in heart rate was 1 bpm for mirabegron 50 mg, and mean increase in systolic blood pressure was 1 mmHg for mirabegron 50 mg. In two Phase 1 studies, including the through QT study 178-CL-077 [and the young/elderly study 178-CL-03]1, BP increases of approximately 3 mmHg were observed for mirabegron 50 mg, and the BP increase with mirabebron appeared to be dose-related. Heart rate increases were also larger in Phase 1 compared to Phase 3.*
- *In the long-term, active-controlled study 178-CL-049, the incidence of serious adverse events of neoplasms was higher in the mirabegron 100 mg group compared to the mirabegron 50 mg group and the active control group: serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with mirabegron 50 mg, mirabegron 100 mg and active control once daily, respectively. The reports were of a wide variety of commonly occurring neoplasms in mirabegron 100 mg subjects (prostate cancer, lung cancer, breast cancer, endometrial cancer, etc). No single neoplasm was reported by more than 2 patients. The meaning of this signal is unclear.*
- *Two significant clinical hepatic adverse events were reported in the NDA, both with possible concomitant allergic phenomena. Both of these cases had confounding factors. In one of these cases, Stevens-Johnson syndrome was reported, along with increased serum ALT, AST and bilirubin in a patient taking mirabegron 100 mg and an acetaminophen-containing herbal medication.*

The risk benefit analysis is, in my opinion, satisfactory for NDA approval. The data provided in the Sponsor's submissions support adequate directions for use, including the data to describe a safe and effective dose. The submissions do allow for labeling that will permit safe and effective use of mirabegron 25 mg and 50 mg daily for the treatment of OAB.

<u>Recommendations for Postmarket Risk Management Activities and Postmarket Studies/Clinical Trials</u>:

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

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

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

international databases. If such a study is attempted and proves difficult logistically, a prospective observational cohort may be required.

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

3. CMC/Device

The Chemistry Review team, Bogdan Kurtyka and Moo Jhong Rhee, had the following final recommendation in their second review dated May 16, 2012:

*"The NDA is now recommended for '**Approval**' from the ONQA perspective ".*

The original CMC review dated April 23, 2012 noted that the blister pack labels did not contain the required manufacturer's name, packer or distributor. The Sponsor submitted revised blister labels on May 11, 2012 that contained "Astellas", resolving that issue.

In a subsequent review dated May 22, 2012, the CMC review team noted that the during the FDA laboratory's assessment of the methods validation, an out-of-specification finding was observed for buylated hydroxytoluene (BHT). The amount of BHT was (b) (4) which was a bit less than the specification of (b) (4). The Chemistry evaluation of this issue was that it does not affect the previous "Approval" recommendation because the BHT specification was defined only for release and the tested product was on storage. According to the chemist, it is expected that during storage, the level of BHT would decrease and the result obtained by the FDA laboratory was expected and acceptable.

The April 23, 2012, CMC review contained the following items of note:

- *There was sufficient information to assure identity, strength, purity and quality of the product.*
- *The Office of Compliance issued an overall recommendation of "Acceptable" for the facilities involved in the application.*
- *Mirabegron is a white crystalline powder, practically insoluble in water and soluble in ethanol.*
- *Mirabegron tablets are oval, extended-release 25 mg and 50 mg, brown or yellow tablets, debossed with "325" or "355" on one side and the Astellas logo on the other side. Mirabegron is released from the tablets over an extended period of time by means of an Oral Controlled Absorption System (OCAS). The main components of the tablets are mirabegron, polyethylene oxide (b) (4) and polyethylene glycol (b) (4) (PEG). Also in the tablets are hydroxypropyl cellulose, (b) (4), butylated hydroxytoluene, magnesium stearate, (b) (4)*
- *Microbial tests ate done on the tablets only in the stability studies at the initial and final timepoints. This is acceptable.*
- *The proposed container closure systems of HDPE bottles with child resistant closures, and blisters with push-through lidding, are adequate*
- *Expiration dating of 24 months (for 25 mg in bottles) and 36 months (for 50 mg in bottles and both strengths in blisters) is acceptable and is granted.*

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewers, Eric Andreasen and Lynnda Reid, made the following recommendation in their final review dated April 12, 2012:

> "*The nonclinical data support **approval** of this product for the treatment of overactive bladder in adult patients with symptoms of urge urinary incontinence, urgency and urinary frequency at a maximum daily dose of 50 mg.*"

There were no additional nonclinical recommendations.

The following are notable comments from the April 12, 2012, Pharmacology/Toxicology review:

- Mirabegron is a beta-3 adrenergic receptor (ß3-AR) agonist. Nonclinical and clinical studies suggest that mirabegron also has some ß1-AR agonist activity.
- Mirabegron was shown to increase bladder capacity and reduce bladder contractions in nonclinical pharmacology studies.
- Mirabegron was readily absorbed and widely distributed in animals. Mirabegron and metabolites were eliminated in urine and feces. Enterohepatic circulation was shown in rats.
- Findings in animals at exposures similar to the maximum recommended human (MHRD) dose (50 mg once daily) were characteristic of the expected beta adrenergic agonist effects and included decreased frequency of urination, slight increase in blood pressure, slight increase in heart rate, and increases in salivation and lacrimation.
- Toxicities observed in nonclinical studies at exposures greater than the MHRD included effects on cardiovascular function, hepatotoxicity, effects on body weight and metabolism, and reproductive/developmental effects.
- Elevated heart rate was observed in rats after IV dosing at exposures < 2-fold the MHRD, in dogs at less than the 1-fold the MHRD, in rabbits at 9-fold the MHRD, and in monkeys at 12-fold the MHRD. Mirabegron-induced increases in HR were partially reversed by ß1-AR antagonist metoprolol, suggesting that at least some of this effect is related to ß1-AR agonism. Ventricular tachycardia was observed in monkeys at 37 times the MHRD.
- Eosinophilic pigment deposition was observed in the livers of rats at exposures 12-17 times the MHRD. Hepatic swelling and fibrosis was observed in rats at lethal exposures >130 times the MHRD. Hepatocyte hypertrophy, vacuolization and lipid accumulation was observed in dogs at 25 times the MHRD. Hepatoxicity was not observed in monkeys.
- At high or lethal exposures (in most species, 21 to 160-fold the MHRD), serious CNS signs including ptosis, staggering, tremor, tonic convulsions, decreased movement, and convulsions, were observed in mice, rats, rabbits and monkeys.
- Mirabegron or its metabolites accumulated in the pigmented tissues of the eye of rats; however, no ophthalmoscopic or histopathologic findings were observed in any animal species at large multiples of the MHRD.
- Fertility was not affected in males or in females below the lethal dose.
- Mirabegron had no effect on development of rat fetuses at exposures up to 6-fold the MHRD, nor in rabbits at clinically relevant exposures. However, rat fetuses exposed to

22-fold the MHRD displayed wavy ribs and decreased ossification. Decreased fetal weight and bone malformations were observed at maternally toxic exposures (96-fold the MHRD). In rabbits, reduced fetal weights were observed at 14-fold the MHRD and cardiomegaly, dilated aortas, and impaired ossification were observed at 36-fold the MHRD.

- Mirabegron was transferred to rat pups in milk.
- Mirabegron exposure was roughly 2-fold greater in pregnant rabbits compared to non-pregnant rabbits.
- Mirabegron was not genotoxic in a standard battery of in vitro and in vivo tests. Mirabegron-related neoplasms were not observed after 2 years of daily exposure in mice exposed to 21-25 times the MHRD or in rats exposed to 25-45 times the MHRD. The reviewer stated, "From a nonclinical perspective, the available nonclinical data suggest that mirabegron is not genotoxic or carcinogenic."

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated May 22, 2012, the Clinical Pharmacology review team of Sayed Al Habet, Christian Grimstein, Michael Pacanowski, Jiang Liu, Yaning Wang, Myong-Jin Kim, and Dennis Bashaw had the following final recommendation:

*"From the Clinical Pharmacology perspective, this NDA is **acceptable**"*

There were no postmarketing requirements or commitments recommended from the Clinical Pharmacology perspective.

In their "*Summary of Clinical Pharmacology and Biopharmaceutics Findings*", Clinical Pharmacology made the following key comments:

- Pharmacokinetics: The median T_{max} is 3-4 hours. Mirabegron is 71% bound to plasma proteins, mostly albumin and alpha-1 acid glycoprotein. The mirabegron concentration in erythrocytes is 2-fold higher than in plasma. The drug is widely distributed in the body. Absolute bioavailability is 29-35%. Steady state is reached within 7 days. The drug is extensively metabolized to approximately 10 metabolites. Approximately 25% is found unchanged in urine. Drug and metabolites are found in both feces and urine. There are multiple metabolic pathways, including dealkylation, oxidation, glucuronidation, and amide hydrolysis. There are multiple enzymes and isoenzymes involved, but the primary responsible enzyme appears to be CYP3A4. The terminal elimination half-life is 50 hours. The exposure is approximately 40-50% higher in females compared to males, but when corrected for body weight, the difference between genders is only approximately 20-30%. Phase 3 studies were conducted in men and in women, with no evidence of different safety between the genders. There is no need for dose adjustment based on gender.

- Food Effect: Mirabegron absorption is dependent on the fat content of food; the reduction in absorption being greater following a low fat meal compared to a high fat meal. The Cmax and AUC are reduced by approximately 45% and 17%, respectively, following a high fat meal compared to fasting. When a low fat meal is consumed, the Cmax and AUC are reduced by 75% and 51%, respectively. The Phase 3 studies were conducted without regard to food intake, with demonstration of acceptable safety and efficacy. Therefore, the expected

fluctuations in mirabegron exposure based on intake of different foods are not expected to affect safety or efficacy and no restrictions on food are needed.

- Specific populations (age, ethnicity, renal impairment, and hepatic impairment): There is no significant difference in mirabegron exposure in relation to age (18-55 years versus 65-80 years).

  A cross-study comparison revealed that exposure in Japanese subjects was higher than exposure in Westerner subjects, although some of this difference may be related to differences in body weight. There was no difference in pK between Caucasian and African Americans.

  In patients with mild, moderate, and severe renal impairment, the AUC increased by 31%, 66%, and 118%, respectively, and the Cmax increased by 6%, 23%, and 92%, respectively, compared to healthy subjects. The maximum dose of mirabegron is 25 mg in patients with severe renal impairment, and use is not recommended in patients with end stage renal disease.

  In patients with mild hepatic impairment (Child-Pugh Class A) the Cmax and AUC were increased by 9% and 19%, respectively; and in moderate hepatic impairment (Child-Pugh Class B) they were increased by 175% and 65%, respectively, compared to healthy subjects, No study was conducted in severe hepatic impairment patients (Child-Pugh Class C). The maximum dose of mirabegron is 25 mg in patients with moderate hepatic impairment, and use is not recommended in patients with severe hepatic impairment.

- Other important clinical pharmacology studies: In addition to studies of basic pharmacokinetics, age effect, food effect, and special populations (renal and hepatic impairment), the NDA also included drug interaction studies, including mirabegron in combination with the strong CYP3A4 inhibitor, ketoconozole; CYP2D6 substrates, such as metoprolol and desipramine; and with potential concomitant urologic drugs, such as Flomax (the alpha-1 adrenergic antagonist, tamsulosin), and VESIcare (the M3 muscarinic receptor antagonist, solifenacin). The Sponsor also conducted studies with digoxin and warfarin, and in extensive and poor metabolizers of CYP2D6.

  - *CYP3A4 inhibitors*: Ketoconazole, as a potent CYP3A4 and P-glycoprotein (P-gp) inhibitor, increased the Cmax and AUC of mirabegron by 45% and 81%, respectively. There is no need for dose reduction with ketoconazole.
  - *CYP3A4 inducers*: Rifampin, a potent enzyme inducer, reduced the mirabegron Cmax and AUC by 35% and 44%, respectively. There is no need for dose reduction with rifampin.
  - *CYP2D6 metabolize status*: There was no difference in mirabegron exposure between CYP2D6 poor metabolizers and CYP2D6 extensive metabolizers. Based on this finding, the sponsor did not conduct an interaction study with CYP2D6 inhibitors. No dose adjustment is needed when the drug is co-administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolizers.
  - *With CYP2D6 substrates*: 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. These results demonstrated that mirabegron is a moderate inhibitor of CYP2D6. Therefore, the product label will advise that when mirabegron is taken in combination with metoprolol, desipramine, and other CYP2D6 substrates especially narrow therapeutic index CYP2D6

substrates, that monitoring is appropriate and the CYP2D6 substrate may require dose adjustment.

- *Digoxin and warfarin:* There was minimal and no effect of mirabegron on digoxin and warfarin, respectively.
- *Tamsulosin and solifenacin:* Tamsulosin is an alpha-1 adrenergic antagonist (alpha-1 blocker) approved for the treatment of symptomatic benign prostatic hypertrophy (BPH). Men with BPH can also have OAB. Although studies have not been conducted to determine the safety or efficacy of mirabegron in men taking alpha-1 blockers for BPH, a drug interaction study with tamsulosin was conducted. The Cmax and AUC of tamsulosin (a CYP2D6 and CYP3A4 substrate) were increased by 60% when co-administered with mirabegron. It was concluded that this increase did not require a dose adjustment for tamsulosin.

  Solifenacin is an M-3 receptor antagonist approved for the treatment of OAB. Although studies have not been conducted to determine the safety or efficacy of solifenacin in combination with mirabegron, a drug interaction study with solifenacin was conducted. The PK parameters of mirabegron were almost the same when administered alone or in combination with solifenacin. There was minimal effect of mirabegron on solifenacin PK, as the Cmax and AUC of solifenacin increased by approximately 23% and 26%, respectively. It was concluded that dose adjustments were not necessary.

6. Clinical Microbiology

In their final review dated March 9, 2012, Bryan Riley and John Metcalfe of the Office of Pharmaceutical Science stated"

"The applicant's response to the deficiency is acceptable and the NDA is now recommended for ***approval*** *on the basis of product quality microbiology."*

In their previous review dated February 2, 2012, the Microbiology team stated that the NDA could not be approved because the Sponsor proposed to (b) (4) for microbial limits and such was unacceptable because microbial testing was part of the drug release specification. Microbiology proposed instead that microbial limits testing could be omitted from finished product testing for batch release, but microbial limits testing should be performed at the initial time point (at minimum) on stability samples. The Sponsor agreed to remove microbial limits testing from the drug product release specification and would perform microbial limits testing on stability samples at the initial and final time points.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The "pivotal" clinical efficacy studies in the mirabegron program were the Phase 3 studies **178-CL-46**, **178-CL-047** and **178-CL-074**.

In study 178-CL-046, eligible subjects were randomized to mirabegron 50 mg, mirabegron 100 mg, placebo, and tolterodine SR 4 mg at 1:1:1:1 ratio. In study 178-CL-047, subjects

were randomized to mirabegron 50 mg, mirabegron 100 mg, and placebo at 1:1:1 ratio. In study 178-CL-074, subjects were randomized to mirabegron 25 mg, mirabegron 50 mg and placebo at 1:1:1 ratio.

All three studies were multinational, multi-center, randomized, double-blind, parallel group, placebo-controlled, Phase 3 studies. Study 178-CL-046 was also active-controlled using tolterodine SR 4 mg and it was conducted entirely in Europe. Study 178-CL-047 was conducted in US and Canada, and study 178-CL-074 was conducted in Europe, US and Canada. Each study included 6 visits: a screening visit, a randomization visit, three visits during the 12-Week treatment period and a follow-up visit. At end of the screening visit, study subjects received medication for a single-blind, 2-week placebo run-in period. Following the placebo run-in period, at Visit 2 (randomization visit), eligible subjects were randomized into a double-blind, placebo and active controlled, 12-week treatment period if they experienced frequency of micturition on an average of ≥ 8 times per 24-hour period during the 3-day micturition diary period, experienced at least 3 episodes of urgency (grade 3 or 4[with grade 4 reflecting urge urinary incontinence]) with or without incontinence during the 3-day micturition diary period and met other inclusion and exclusion criteria.
In addition to these three, 12-week, placebo-controlled studies, the NDA also contained study 178-CL-049, a large, multi-national, randomized, 52-Week, double-blind, active-controlled study comparing mirabegron 50 mg and 100 mg once daily to tolterodine LA 4 mg once daily. Although safety was the primary objective in this study, efficacy was also collected.

The NDA also contained results from a number of "non-pivotal" Phase 2 studies; several Phase 2 and 3 studies conducted outside the U.S. and Canada, primarily in Japan; and a host of Phase 1 studies.

7.2 DEMOGRAPHICS

In all studies, the majority of subjects were White (99% for Study 046, 88% for Study 047, and 91% for Study 047). The percentages of White subjects were comparable across treatment groups in each study. The majority of subjects were also female (72% for Study 178 046, 75% for Study 047, and 69% for Study 074). The mean age of subjects was 59 years in Study 046, 60 years in Study 047, and 59 years in Study 074. Overall, the demographics across treatment groups were similar in each study.

7.3 DISPOSITION OF SUBJECTS

The disposition of study patients is summarized in Tables 1 to 4. In study 178-CL-046, a total of 1987 patients were randomized to the four treatment groups and the study discontinuation rate was 9.9%, ranging from 8.9% to 11.5% across the treatment groups. In study 178-CL-047, a total of 1329 patients were randomized to the three treatments and the study discontinuation rate was 13.6%, ranging from 12.2% to 15.2% across the treatment groups. In study 178-CL-047, a total of 1306 patients were randomized to the three treatment groups and the study discontinuation rate was 12.7%, ranging from 10.6% to 15.2% across the treatment groups. For all studies, the most common reasons for discontinuation from the study were adverse events and withdrawal of consent.

Table 1: Summary of Subject Disposition – Study 178-CL-046

	Placebo n (%)	Mirabegron 50 mg n (%)	Mirabegron 100 mg n (%)	Tolterodine SR 4 mg n (%)
Randomized	497 (100.0)	497 (100.0)	498(100.0)	495 (100.0)
Discontinued from study	44 (8.9)	57 (11.5)	45 (9.0)	50(10.1)
Eligibility criterion not met	5 (1.0)	8(1.6)	0	4(0.8)
Adverse event	13(2.6)	25(5.0)	16(3.2)	24(4.8)
Lack of Efficacy	5(1.0)	6(1.2)	2(0.4)	3(0.6)
Withdrew consent	11(2.2)	9(1.8)	17(3.4)	9(1.8)
Lost to follow-up	4(0.8)	3(0.6)	2(0.4)	5(1.0)
Protocol violation	2(0.4)	3(0.6)	5(1.0)	3(0.6)
Randomized but never received study drug	2(0.4)	1(0.2)	1(0.2)	0
Other	2(0.4)	2(0.4)	2(0.4)	2(0.4)

Table 2: Summary of Subject Disposition – Study 178-CL-047

	Placebo n (%)	Mirabegron 50 mg n (%)	Mirabegron 100 mg n (%)
Randomized	454 (100.0)	442 (100.0)	433(100.0)
Discontinued from study	69 (15.2)	59 (13.3)	53 (12.2)
Eligibility criterion not met	0	0	1(0.2)
Adverse event	17(3.7)	18(4.1)	19(4.4)
Lack of Efficacy	9(2.0)	1(0.2)	5(1.2)
Withdrew consent	29(6.4)	22(5.0)	16(3.7)
Lost to follow-up	2(0.4)	9(2.0)	3(0.7)
Protocol violation	7(1.5)	4(0.9)	5(1.2)
Randomized but never received study drug	1(0.2)	0	0
Other	4(0.9)	5(1.1)	4(0.9)

Table 3: Summary of Subject Disposition – Study 178-CL-074

	Placebo n (%)	Mirabegron 25 mg n (%)	Mirabegron 50mg n (%)
Randomized	433 (100.0)	433 (100.0)	440(100.0)
Discontinued from study	66 (15.2)	46 (10.6)	54 (12.3)
Eligibility criterion not met	1(0.2)	1(0.2)	0
Adverse event	15(3.5)	17(3.9)	12(2.7)
Lack of Efficacy	11(2.5)	4(0.9)	3(0.7)
Withdrew consent	20(4.6)	12(2.8)	18(4.1)
Lost to follow-up	4(0.9)	3(0.7)	3(0.7)
Protocol violation	5(1.2)	3(0.7)	8(1.8)
Randomized but never received study drug	0	1(0.2)	0
Other	10(2.3)	5(1.2)	10(2.3)

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

In all three Phase 3 studies, the primary efficacy assessment measures were the same. There were two co-primary efficacy endpoints:

1) Change from baseline to end of treatment (final visit) in mean number of micturitions per 24 hours, and

2) Change from baseline to end of treatment (final visit) in mean number of incontinence episodes per 24 hours.

These are the current standard for primary efficacy endpoints in Phase 3 OAB trials.

The data for the co-primary endpoints were generated from 3-day patient micturition diaries completed by patients themselves at the following time points: prior to the screening visit, prior to the randomization visit, and prior to each on-treatment visit. Times of micturition, incontinence episodes, urgency severity, pad use, and volume voided (2 out of 3 days), were recorded in the diaries.

The pre-defined key secondary efficacy endpoints were:

- change from baseline to end of treatment (final visit) in mean volume voided per micturition,
- change from baseline to Week 4 in mean number of micturitions per 24 hours, and
- change from baseline to Week 4 in mean number of incontinence episodes per 24 hours.

In addition to these key secondary endpoints, other secondary efficacy endpoints included:

- change from baseline in mean level of urinary urgency,
- change from baseline in mean number of urge incontinence episodes per 24 hours,
- change from baseline in mean number of urgency episodes (defined as grades 3 or 4 on the urgency severity scale) per 24 hours,
- change from baseline to end of treatment (final visit) in nocturia episodes per 24 hours,
- change from baseline in "responder" rates:
    - $\geq$ 50% reduction in incontinence episodes
    - $\leq$ 8 micturitions per 24 hours
- change from baseline in the treatment satisfaction – visual analogue scale (TS-VAS)

In analyzing the data from the co-primary endpoints and the key secondary endpoints, a stepwise parallel gate-keeping procedure was employed to control the type I error rate over multiple active treatment groups and multiple efficacy endpoints. The stepwise parallel gate-keeping procedure was performed in the following ordered stages. The first 5 stages were common in all three studies, and stages 6-8 were specific for Study 074.

Stage 1: incontinence episodes at final visit
Stage 2: micturitions at final visit
Stage 3: volume voided per micturition at final visit
Stage 4: incontinence episodes at Week 4
Stage 5: micturitions at Week 4
Stage 6: mean level of urgency at final visit
Stage 7: urgency incontinence episodes at final visit
Stage 8: urgency episodes (grades 3 or 4) at final visit

In the gate-keeping procedure, only after a mirabegron dose achieved statistically significance at the 0.05 significance level at all previous stages could this dose group proceed to the next stage. Within each stage, the Hochberg procedure was used to control the overall stage Type I error rate at α =0.05 level for multiple treatment group comparisons.

7.4.1.1 Primary Efficacy Analysis

In all three phase 3 studies, all tested mirabegron doses (25 mg, 50 mg, and 100 mg) demonstrated statistically significant improvement in both co-primary endpoints compared to placebo, using the pre-specified hierarchal testing procedure.

The doses requested for approval are 25 mg and 50 mg. In pooled efficacy analyses, treatment with mirabegron 25 mg and 50 mg resulted in changes from baseline in incontinence episodes per 24 hours as compared to placebo of -0.40 (p 0.005) and -0.40 (p <0.001), respectively, and changes in micturitions per 24 hours as compared to placebo of -0.47 (p 0.007) and -0.75 (p <0.001), respectively.

In study 046, the mean, placebo-subtracted changes were:

- -0.41 and -0.29 for mirabegron 50 mg and 100 mg, respectively, for incontinence episodes, and
- -0.60 and -0.44 for mirabegron 50 mg and 100 mg, respectively, for micturitions.

In study 047, the mean, placebo-subtracted changes were:

- -0.34 and -0.50 for mirabegron 50 mg and 100 mg, respectively, for incontincence episodes, and
- -0.61 and -0.70 for mirabegron 50 mg and 100 mg, respectively for micturitions.

In study 074, the mean, placebo-subtracted changes were:

- -0.40 and -0.42 for mirabegron 25 mg and 50 mg, respectively, for incontincence episodes, and
- -0.47 and -0.42 for mirabegron 25 mg and 50 mg, respectively for micturitions.

These data, along with data for the key secondary efficacy endpoint, volume voided, are shown in the following set of tables:

Table 4: Summary of Primary and Key Secondary Efficacy Endpoint – Study 178-CL-046

	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Mean Number of Incontinence Episodes per 24 Hours (FAS-I) at final visit			
N	291	293	281
Mean	1.54	1.22	1.37
Change from baseline*	-1.17	-1.57	-1.46
Difference vs. placebo (p-value†)		-0.41 (0.003#)	-0.29 (0.01#)
Mean Number of Micturitions per 24 Hours (FAS) at final visit			
N	480	473	478
Mean	10.35	9.70	9.76
Change from baseline*	-1.34	-1.93	-1.77
Difference vs. placebo (p-value‡)		-0.60 (<0.001#)	-0.44 (0.005#)
Mean Volume Voided (mL) per Micturition (FAS) at final visit			
N	480	472	478
Mean	169.1	185.2	183.8
Change from baseline*	12.3	24.2	25.6
Difference vs. placebo (p-value‡)		11.9 (<0.001#)	13.2 (<0.001#)

FAS: Full Analysis Sample; FAS-I: Full Analysis Sample-Incontinence
**Change from baseline was obtained from an ANCOVA model.*

†p-values from pair-wise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡p-values from pair-wise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior compared to placebo with multiplicity adjustments at the 0.05 level.

Table 5: Summary of Primary and Key Secondary Efficacy Endpoints – Study 178-CL-047

Efficacy Endpoint	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Mean Number of Incontinence Episodes per 24 Hours (FAS-I) at final visit			
N	325	312	296
Mean	1.81	1.33	1.14
Change from baseline*	-1.13	-1.47	-1.63
Difference vs. placebo (p-value†)		-0.34 (0.026#)	-0.50 (<0.001#)
Mean Number of Micturitions per 24 Hours (FAS) at final visit			
N	433	425	412
Mean	10.51	10.09	9.91
Change from baseline*	-1.05	-1.66	-1.75
Difference vs. placebo (p-value‡)		-0.61 (0.001#)	-0.70 (< 0.001#)
Mean Volume Voided (mL) per Micturition (FAS) at final visit			
N	433	424	412
Mean	164.6	174.4	175.4
Change from baseline*	7.0	18.2	18.0
Difference vs. placebo (p-value‡)		11.1 (0.001#)	11.0 (0.002#)

FAS: Full Analysis Sample; FAS-I: Full Analysis Sample-Incontinence
**Change from baseline was obtained from an ANCOVA model.*
†p-values from pairwise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡ p-values from pairwise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior to placebo with multiplicity adjustments at the 0.05 level.

Table 6: Summary of Primary and Key Secondary Efficacy Endpoints – Study 178-CL-074

Efficacy Endpoint	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Mean Number of Incontinence Episodes per 24 Hours (FAS-I) at final visit			
N	26	254	257
Mean	1.5	1.21	1.13
Change from baseline*	-	-1.36	-1.38
Difference vs. placebo (p-value†)		-0.40 (0.005#)	-0.42 (0.001#)
Mean Number of Micturitions per 24 Hours (FAS) at final visit			
N	41	410	426
Mean	10.3	10.02	10.04
Change from baseline*	-	-1.65	-1.60
Difference vs. placebo (p-value‡)		-0.47 (0.007#)	-0.42 (0.015#)
Mean Volume Voided (mL) per Micturition (FAS) at final visit			
N	41	410	426
Mean	172.	177.6	180.3
Change from baseline*	8.	12.8	20.7
Difference vs. placebo (p-value‡)		4.6 (0.15)	12.4 (<0.001#)

FAS: Full Analysis Sample; FAS-I: Full Analysis Sample-Incontinence

**Change from baseline was obtained from an ANCOVA model.*
†p-values from pairwise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡ p-values from pairwise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior to placebo with multiplicity adjustments at the 0.05 level.

Results from the preplanned secondary efficacy assessments, such as the mean volume voided per micturition, the mean level of urinary urgency, mean urgency severity, mean urge incontinence episodes, "responder" rates for incontinence and episodes micturitions, and treatment satisfaction were supportive of the clinical meaningfulness of the primary endpoint results.

For the 50 mg dose, the mean volume voided was statistically significantly different from placebo in all three studies. For the 25 mg dose, which was tested only in Study 074, the increase in mean volume voided was smaller than that observed for 50 mg (13 mL vs 21 mL, respectively) and the difference between 25 mg and placebo was not statistically significant.

Also, the 50 mg dose achieved statistical significance compared to placebo for both co-primary endpoints at Week 4. Because the 25 mg dose did not achieve statistical significance for volume voided, formal testing for efficacy at Week 4 was not allowed, as per the pre-defined hierarchical testing procedure. At Week 4, however, the 25 mg dose showed differences from placebo, which achieved the following p values in exploratory statistical comparisons: for incontinence episodes (p 0.039) and for micturitions ($p < 0.001$).

7.4.1.2 Dose Selection Rationale

In selecting a final dose for approval, it was noted that the co-primary efficacy endpoint results from study 178-CL-074 demonstrated comparability for the 25 mg and 50 mg doses at Week 12. However, the 25 mg dose did not demonstrate a statistically significant difference from placebo for the key secondary endpoint volume voided per micturition. Thus, the subsequent secondary endpoints in the pre-defined statistical hierarchy, including incontinence episodes and micturitions at Week 4, could not undergo formal statistical testing for the 25 mg dose. Nevertheless, all data for mirabegron 25 mg was still extensively analyzed. The results showed clear separation for the 25 mg from placebo for the micturitions and incontinence episode frequency endpoints at Week 4 (p 0.039), with almost identical results of the 25 mg dose to the 50 mg dose by Week 8 and maintained to Week 12 (see Figures 1 and 2).

Figure 1: Change from Baseline at Each Visit in Mean Number of Incontinence Episodes per 24 Hours – Study 178-CL-074, FAS-I

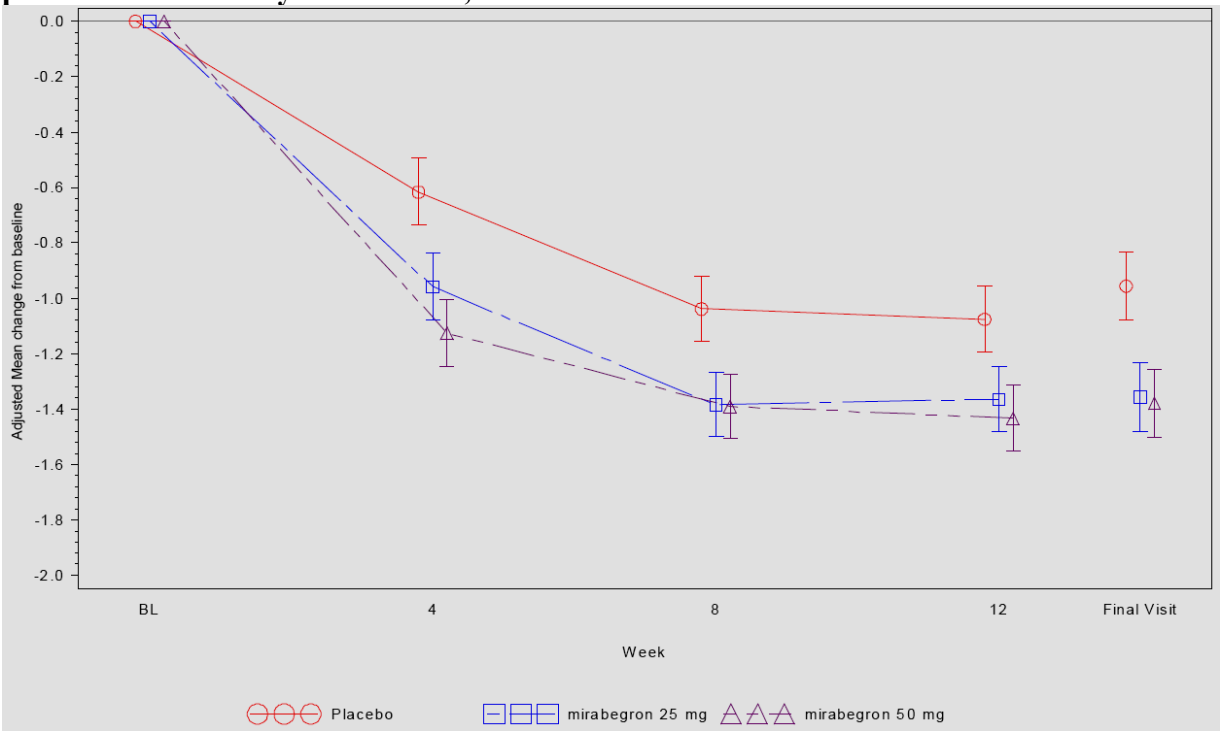
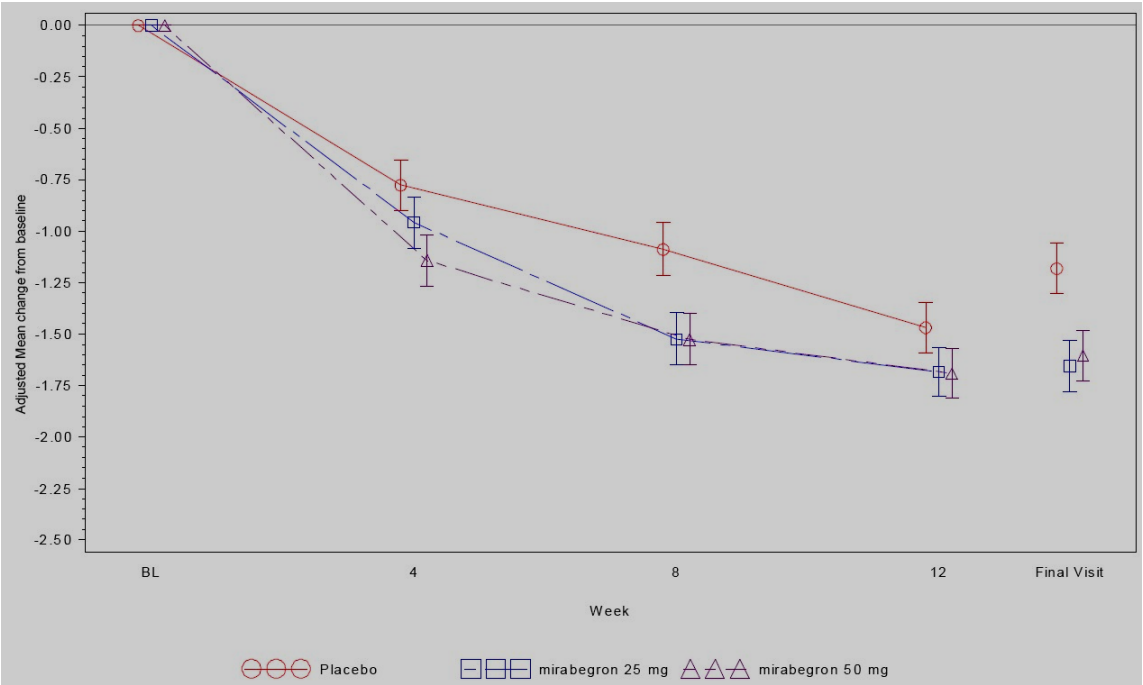


Figure 2: Change from Baseline at Each Visit in Mean Number of Micturitions per 24 Hours –Study 178-CL-074, FAS



Although the data from Study 074 demonstrate comparability of efficacy for the 25 mg dose and 50 mg dose for the co-primary endpoints at Week 12, there was evidence for greater clinical benefit for the 50 mg dose when secondary endpoints were considered. For example, the storage capacity of the bladder was improved, as demonstrated by a larger improvement in mean volume voided per micturition for 50 mg compared to 25 mg. Additional evidence in favor of 50 mg includes:

- Overall mirabegron 50 mg achieved more statistically significant endpoints than mirabegron 25 mg.
- With respect to mean level of urgency and mean number of Grade 3 or 4 urgency episodes, while both mirabegron 25 and 50 mg numerically improved these measures, the improvement with mirabegron 50 mg was numerically greater than the 25 mg dose.
- An urgency responder was defined as a patient with a decrease from baseline to final visit in mean level of urgency as large as the Sponsor's determination of minimally important difference (0.24). At the final visit, the percentage of responders defined this way was 3.9% for the mirabegron 25 mg group and 8.3% for the mirabegron 50 mg group. Statistical significance was achieved only for the mirabegron 50 mg group.
- In incontinent patients who required pad use, 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. Statistical significance was achieved only for the mirabegron 50 mg group.
- Clinical and Patient Global questions suggest some degree of superiority for the 50 mg dose over the 25 mg dose.
- On the WPAI:SHP (Work Productivity and Activity Impairment), a negative change from baseline indicates improvement. Four parameters were assessed: work time missed, impairment while working, overall work impairment and activity impairment. The negative mean change from baseline to week 12 and final visit was greater in the mirabegron 50 mg group compared to placebo for all parameters except for overall work impairment.

CDTL Comment: *Taken together, the data demonstrates similar primary efficacy results for mirabegron 25 mg and 50 mg at 8 weeks, but greater overall clinical benefit for mirabegron 50 mg. Therefore, in order to optimize the risk/benefit ratio, a starting dose of 25 mg for all patients, followed by an increase to mirabegron 50 mg in patients with suboptimal improvement in symptoms seems reasonable and appropriate. The prescriber should be aware that it may take 8 weeks to achieve optimal results with mirabegron 25 mg.*

Statistician's Conclusion

In their final memo for this NDA, dated June 7, 2012, the Statistical Review team of Jia Guo and Mahboob Sobhan concluded the following:

> "*The purpose of this review is to evaluate the efficacy data in support of mirabegron in the treatment of OAB. Based on reviewer's analyses, the results supported the efficacy of mirabegron 25 mg, 50 mg and 100 mg in the improvement of all two protocol specified co-primary endpoints. The treatment effects of both mirabegron 25 mg and 50 mg dose were very similar on both co-primary endpoints.*
>
> *From a statistical perspective, all doses of mirabegron (25 mg 50 mg, and 100 mg) were effective in treating OAB. Based on the efficacy analyses, mirabegron 25 mg should be considered for general OAB patients as well.*"

The Statistical review focused on the Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety studies 178-CL-046, 178-CL-047 and 178-CL-074. The designs, endpoints and results for these 3 studies have already been discussed. Study 046 included dose of mirabegron of 50 mg and 100 mg, as well as a dose of tolterodine LA of 4 mg. Study 047 again included mirabegron doses of 50 mg and 100 mg. Study 074 was the only study to include the mirabegron 25 mg dose, in addition to the 50 mg dose.

The Statistics review team confirmed that all doses tested in all three studies met the 2 co-primary endpoints at a p value < 0.05 using an appropriate ANCOVA model for the analysis. No statistical issues were identified in the submission.

One issue of note in the Statistical review was the effectiveness of the 25 mg dose in comparison to the 50 mg dose. The Statistical review team noted that although mirabegron 50 mg was the single dose proposed for approval by the Applicant, mirabegron 25 mg dose showed very similar efficacy for the co-primary endpoints as compared to mirabegron 50 mg in Study 178-CL-074, a Phase 3 trial with adequate sample size. The 25 mg achieved statistically significant efficacy by Week 8 and maintained that efficacy until study completion at Week 12. Therefore, the Statistical review team recommended that mirabegron 25 mg be considered for approval in general OAB patients in addition to the 50 mg dose.

The Statistical team also noted that there was no difference observed in treatment effect between US/Canada and European patients.

Finally, the Statistical team conducted subgroup analyses by age, gender, race, and concomitant use of beta-adrenergic blockers. The following was observed:

- In all three studies, the treatment effect on the change from baseline in incontinence episodes and in micturitions (except for the 50 mg dose group in Study 046) were numerically larger in subjects who were ≥ 65 years old than subjects who were < 65 years old.
- The percentage of non-White subject was too small to draw meaningful conclusions.
- No consistent impact of beta-blocker use was observed on the treatment effect of mirabegron with respect to the co-primary efficacy endpoints.

7.4.2 Overall Assessment of Efficacy

In three, randomized, double-blind, 12-week, placebo-controlled studies, mirabegron 50 mg demonstrated efficacy in the treatment of OAB, as demonstrated by success on the co-primary endpoints and most of the secondary endpoints. In Study 178-CL-074, mirabegron 25 mg also demonstrated efficacy for the treatment of OAB. The treatment effect for both doses is highly statistically significant compared to placebo and based upon a number of secondary endpoints and secondary analyses, the effect of mirabegron on OAB is considered to be clinically meaningful.

In regard to dose selection, taken together, the data demonstrates benefit for both doses at Week 4, and similar primary efficacy results for mirabegron 25 mg and 50 mg at Week 8, but there is evidence for greater overall clinical benefit for mirabegron 50 mg compared to 25 mg. Therefore, in order to optimize the risk/benefit ratio, a starting dose of 25 mg for all patients, followed by an increase to mirabegron 50 mg in patients with suboptimal improvement in symptoms seems reasonable and appropriate. The prescriber should be aware that it may take up to 8 weeks to achieve optimal results with mirabegron 25 mg.

8. Safety

8.1 SAFETY DATA

The safety data submitted in the mirabegron NDA come from:

1. Three (3), 12-week, Phase 3, controlled efficacy and safety OAB studies (178-CL-046, 178-CL-047, and 178-CL-074). The Sponsor refers to this grouping as the "*EU/NA OAB 12-Week*" population, and this is the principal, short-term, controlled population used for FDA review;

2. A 52-week, active-controlled, safety study (178-CL-049). Sponsor refers to this study as "*EU/NA Long-Term Controlled Population*". This is the principal long-term, controlled population used for FDA review;

3. Two (2), 12-week, Phase 2 OAB studies, and one 12-Week Japanese Phase 3 OAB study (178-CL-044, 178-CL-045, and 178-CL-048, respectively). When combined with Studies -046, -047 and -074, the Sponsor refers to this grouping as the "*Global OAB 12-Week Phase 2 and 3 Population*";

4. Six (6) additional Phase 2 and 3 controlled studies of mirabegron in a variety of conditions (type 2 diabetes, lower urinary tract symptoms/bladder outlet obstruction), using the IR or OCAS formulations, administered in at least one dose, and conducted in a host of countries. When combined with the six OAB studies, the Sponsor refers to this grouping as the "*Global Phase 2 and 3*" population.

5. Twenty-six (26) Phase 1 studies of pharmacokinetics (pK), clinical pharmacology, and tolerability. These studies included: investigations of single and multiple dose pK, food effect, metabolic drug interactions (e.g, inhibitors of CYP3A4), and avanafil pK in specific populations (e.g., renal and hepatic impaired).

6. A number of special safety studies, as follows:
    a. a thorough QT study (178-CL-077)
    b. an intraocular pressure study (178-CL-081)
    c. a cardiovascular interaction study (178-CL-080)

In total, 5863 subjects were exposed to mirabegron during the clinical development program. In the EU/NA OAB-12 Week Population, which is the principal controlled population used by FDA for efficacy and safety analyses, a total of 2736 patients received mirabegron. In the long-term study 178-CL-049, a total of 1632 subjects were exposed to mirabegron. In total, 1572 subjects were exposed to mirabegron for ≥ 6 months (182 days) and 622 subjects were exposed to avanafil for ≥ 12 months (365 days).

The doses for marketing will be 25 mg and 50 mg. There is a large amount of safety information from Phase 3 studies in OAB patients at the higher dose of 100 mg (n=929), as well as data from Phase 2 at the even higher dose of 200 mg (n= 167). In the long-term safety study (52 weeks), 810 subjects with OAB received the 100 mg dose.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

Deaths

There were 11 deaths in the mirabegron program, including 2 deaths in ongoing Study 178-CL-090. In this ongoing study, one death occurred on blinded treatment and one occurred prior to randomization. Thus, nine deaths occurred in patients participating in completed trials; 5 in mirabegron patients, one in a placebo patient, and 3 in tolterodine patients.

Among the 5 deaths in mirabegron patients, the causes of death were: 1) metastatic colon cancer (Day 99 in Study 047), 2) methicillin-reistant staph aureus (MRSA) pneumonia with acute respiratory failure (Day 108 in Study 049), 3) cardiac failure (Day 190 in Study 049), 4) completed suicide (Day 266 in Study 049), and 5) aortic dissection (Day 237 in Study 51).

***CDTL Comment**: None of the deaths could be attributed to mirabegron.*

Serious Adverse Events (SAEs)

The incidence of serious adverse events (SAEs) in the combined ***EU/NA, 12-Week, Phase 3 studies*** was *2.1%* (29/1380), *1.6%* (7/432), *2.1%* (29/1375), and *2.8%* (26/929) in the placebo, mirabegron 25 mg, mirabegron 50 mg and mirabegron 100 groups, respectively. The incidence of SAEs in the tolterodine group was *2.2%* (11/495). SAEs reported by more than 1 subject in any group were:

- placebo: chest pain (n=2; 0.1%).
- mirabegron 25 mg: no SAE reported by more than 1 subject.
- mirabegron 50 mg: atrial fibrillation (n=3; 0.3%), and prostate cancer (n=2; 0.2%).
- mirabegron 100 mg: chest pain (n=3; 0.3%), atrial fibrillation (n=2; 0.2%), prostate cancer (n=2; 0.2%), and bunion operation (n=2; 0.2%).
- tolterodine: no SAE reported by more than 1 subject.

In these combined pivotal studies, a slight difference was observed between mirabegron and placebo in the total number of neoplasms reported as SAEs when a variety of differing tumors (breast cancer, bladder cancer, Bowen's disease. metastatic colon cancer, lung cancer, malignant melanoma, and prostate cancer), each reported by 1 patient [except for prostate cancer, n=2], were added together. The incidence of SAEs in the Neoplasm category were *0.1%* (1/1380), *0.1%* (1/432), *0.2%* (3/1375), and *0.3%* (3/929) in the placebo, mirabegron 25 mg, mirabegron 50 mg and mirabegron 100 groups, respectively. The incidence of Neoplasm SAEs in the tolterodine group was *0.2%* (1/495). The difference between mirabegron and placebo in this category was driven by results in one study (178-CL-047), and mostly by the 100 mg group. When these cases were analyzed (the reader is referred to the medical officer's review for individual case narratives), most were evaluated as pre-existing lesions.

CDTL Comments*:*

1. *The few SAEs of atrial fibrillation in these "pivotal" studies were confounded by pre-existing atrial fibrillation and potential inciting agents, making attribution to mirabegron problematic.*
2. *The small difference between mirabegron and placebo in Neoplasms appears driven by the 100 mg group in one of these 12-week studies (Study 047). Most tumors appeared to have been pre-existing.*

The incidence of serious adverse events (SAEs) in the ***EU/NA, 52-Week, Active-Controlled Study*** (Study 049) was *5.2%* (42/812), *6.2%* (51/820), and *5.4%* (44/812) in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively. SAEs reported by more than 1 subject in any group were:

- mirabegron 50 mg: cerebrovascular accident (n=3; 0.4%), atrial fibrillation (n=2; 0.2%), and osteoarthritis (n=2; 0.2%),
- mirabegron 100 mg: liver function test abnormal (n=2; 0.2%), breast cancer (n=2, 0.2%), lung neoplasm malignant (n=2, 0.2%), and prostate cancer (n=2; 0.2%).
- tolterodine: atrial fibrillation (n=3; 0.4%) and breast cancer (n=2; 0.2%).

In Study 178-CL-049, a difference was observed between mirabegron 100 mg and mirabegron 50 mg and tolterodine in the total number of neoplasms reported as SAEs. The incidence of SAEs in the Neoplasm category were *0.1%* (1/812), *1.3%* (11/820), and *0.5%* (4/812) in the mirabegron 50 mg, mirabegron 100 mg and tolterodine groups, respectively. The only tumors reported by more than 1 subject were breast cancer (n=2, in both mirabegron 100 mg and tolterodine groups), lung neoplasm malignant (n=2, mirabegron 100 mg), and prostate cancer (n=2, mirabegron 100 mg). When these cases were analyzed (the reader is referred to the medical officer's review for individual case narratives), most appeared to be pre-existing lesions.

CDTL Comments:

1. *Overall, the incidence of SAEs was quite low.*
2. *All patients who sustained a CVA had significant pre-existing risk factors for CVA*

3. *In all cases of atrial fibrillation, confounding factors that could incite atrial fibrillation were present. This consideration, along with the small number of cases, precludes attribution of atrial fibrillation to mirabegron.*
4. *The incidence of neoplasms reported as SAEs is greater for mirabegron 100 mg compared to mirabegron 50 mg and to tolterodine ER 4 mg. Most, and perhaps all, of these cases were pre-existing conditions (see the medical officer's extensive discussion of each case). There is wide variety of tumor types. The clinical significance of this finding is unknown. It should be noted that there was only 1 neoplastic SAE reported for the to-be-marketed dose 50 mg, and mirabegron 50 mg actually had a lower frequency of such reports compared to tolterodine. The clinical significance of the finding will be further evaluated in a Phase 4 electronic database epidemiologic cohort study.*

Discontinuations due to Adverse Events

In the ***EU/NA, 12-Week, OAB studies*** (the "pivotal" studies), the incidences of adverse events leading to study discontinuation were *3.3%* (46/1380) for placebo versus *3.8%* (104/2736) for the mirabegron 25 mg, 50 mg, and 100 mg dose groups combined. In the combined mirabegron group, the most commonly reported AEs leading to study discontinuation were hypertension (n=6) tachycardia (n=4), AST/ALT increased (n=3), edema peripheral (n=3), atrial fibrillation (n=3), and bilirubin increased, liver function test abnormal, and "hypertensive crisis" (n=2 each). No other AE led to study discontinuation in more than 1 patient.

By dose group, the incidence of AEs leading to study discontinuation in these pivotal was 3*.3%* (46/1380), *3.9%* (17/432), *3.9%* (53/1375), and *3.7%* (34/929) in the placebo, mirabegron 25 mg, mirabegron 50 mg and mirabegron 100 groups, respectively. The incidence of AEs leading to study discontinuation in the tolterodine group was *4.4%* (22/495). AEs leading to study discontinuation reported by more than 2 subjects in any group were:

- placebo: nausea (n=8, 0.6%); headache (n=5, 0.4%); vomiting (n=3, 0.2%); constipation (n=3, 0.2%) and chest pain (n=3, 0.2%).
- mirabegron 25 mg: hypertension (n=2. 0.5% [vs 0.2% for placebo]).
- mirabegron 50 mg: headache (n=4, 0.3%); nausea (n=3, 0.2%), and diarrhea (n=3, 0.2% [vs 0% for placebo]).
- mirabegron 100 mg: constipation (n=3; 0.3% [vs 0.2% for placebo]).
- tolterodine: no AE reported to lead to study discontinuation in more than 2 subjects.

The incidence of AEs leading to study discontinuation in the ***EU/NA, 52-Week, Active-Controlled Study*** was *5.9%* (48/812), *6.1%* (50/820), and *5.7%* (46/812) in the mirabegron 50 mg, mirabegron 100 mg, and tolterodine groups, respectively. In the combined mirabegron group, the most commonly reported AEs leading to study discontinuation were hypertension (n=6), fatigue (n=4), and lung neoplasm malignant, prostate cancer, pruritis, rash, urticaria, "pain", and "hypertensive crisis" (n=2 each). No other AE led to study discontinuation in more than 1 patient. AEs leading to study discontinuation reported by more than 2 subjects in any group are shown by treatment group in Table 7 below.

Table 7: AEs Leading to Study Discontinuation by at Least 2 Patients in Any Dose Group, EU/NA Long-Term Controlled Population (Study 178-CL-049)

MedDRA (v12.1) SOC PT †, n (%) of Patients	Mirabegron 50 mg (n = 812)	Mirabegron 100 mg (n = 820)	Mirabegron Total Mirabegron (n = 1632)	Tolterodine ER 4 mg (n = 812)
Overall	48 (5.9%)	50 (6.1%)	98 (6.0%)	46 (5.7%)
Cardiac disorders	4 (0.5%)	4 (0.5%)	8 (0.5%)	7 (0.9%)
Palpitations	0	2 (0.2%)	2 (0.1%)	0
Ear and labyrinth disorders	0	2 (0.2%)	2 (0.1%)	2 (0.2%)
Vertigo	0	2 (0.2%)	2 (0.1%)	1 (0.1%)
Eye disorders	5 (0.6%)	3 (0.4%)	8 (0.5%)	3 (0.4%)
Dry eye	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Vision blurred	3 (0.4%)	1 (0.1%)	4 (0.2%)	1 (0.1%)
Gastrointestinal disorders	14 (1.7%)	9 (1.1%)	23 (1.4%)	11 (1.4%)
Abdominal pain	1 (0.1%)	2 (0.2%)	3 (0.2%)	0
Abdominal pain upper	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)
Constipation	7 (0.9%)	2 (0.2%)	9 (0.6%)	0
Dry mouth	3 (0.4%)	1 (0.1%)	4 (0.2%)	4 (0.5%)
Gastritis	2 (0.2%)	0	2 (0.1%)	1 (0.1%)
Nausea	3 (0.4%)	2 (0.2%)	5 (0.3%)	1 (0.1%)
General disorders and administration site conditions	4 (0.5%)	5 (0.6%)	9 (0.6%)	2 (0.2%)
Fatigue	1 (0.1%)	3 (0.4%)	4 (0.2%)	1 (0.1%)
Pain	2 (0.2%)	0	2 (0.1%)	0
Infections and infestations	6 (0.7%)	2 (0.2%)	8 (0.5%)	3 (0.4%)
UTI	3 (0.4%)	0	3 (0.2%)	1 (0.1%)
Investigations	1 (0.1%)	3 (0.4%)	4 (0.2%)	4 (0.5%)
Liver function test abnormal	0	2 (0.2%)	2 (0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	7 (0.9%)	7 (0.4%)	1 (0.1%)
Lung neoplasm malignant	0	2 (0.2%)	2 (0.1%)	0
Prostate cancer	0	2 (0.2%)	2 (0.1%)	0
Nervous system disorders	10 (1.2%)	8 (1.0%)	18 (1.1%)	10 (1.2%)
Dizziness	4 (0.5%)	2 (0.2%)	6 (0.4%)	0
Headache	5 (0.6%)	4 (0.5%)	9 (0.6%)	3 (0.4%)
Renal and urinary disorders	2 (0.2%)	4 (0.5%)	6 (0.4%)	4 (0.5%)
Dysuria	0	2 (0.2%)	2 (0.1%)	0
Skin and subcutaneous tissue disorders	2 (0.2%)	5 (0.6%)	7 (0.4%)	1 (0.1%)
Pruritus	0	2 (0.2%)	2 (0.1%)	0
Rash	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Urticaria	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Vascular disorders	4 (0.5%)	3 (0.4%)	7 (0.4%)	4 (0.5%)
Hypertension	4 (0.5%)	2 (0.2%)	6 (0.4%)	3 (0.4%)

CDTL Comments:

1. *Overall, the incidence of AEs leading to study discontinuation was quite low.*
2. *In the majority of cases of hypertension leading to study discontinuation, hypertension was present at baseline.*

8.1.2 Other Adverse Events

Overall Adverse Events

In the combined Phase 3 studies 178-CL-046, 178-CL-047 and 178-CL-074, the commonly reported TEAEs (incidences ≥3% in the total mirabegron groups) were:

- *Hypertension* (placebo, 7.6%; mirabegron 25 mg, 11.3%; mirabegron 50 mg, 7.3%; mirabegron 100 mg, 7.3%, and tolterodine 8.1%);
- *Nasopharyngitis* (placebo, 2.5%; mirabegron 25 mg, 3.5%; mirabegron 50 mg, 3.9%; mirabegron 100 mg, 3.4%, and tolterodine 2.8%); and
- *UTI* (placebo, 1.8%; mirabegron 25 mg, 4.2%; mirabegron 50 mg, 2.9%; mirabegron 100 mg, 3.0%, and tolterodine 2.0%)

The list of AEs reported by ≥ 1% of mirabegron subjects and exceeding placebo rate in the Phase 3 studies 178-CL-046, 178-CL-047 and 178-CL-074 is shown in Table 8 below.

Table 8: Percentages of Patients with Adverse Events Reported by ≥1% Mirabegron Patients and Exceeding Placebo Rate in the EU/NA, 12-Week, OAB Population (Studies 178-CL-046, -047, and -074)

	Placebo (%)	**Mirabegron 25 mg (%)**	**Mirabegron 50 mg (%)**	**Mirabegron 100 mg (%)**	**Tolterodine LA, 4 mg (%)**
No. of Patients	**1380**	**432**	**1375**	**929**	**495**
Hypertension	7.6	11.3	7.5	5.2	8.1
Nasopharyngitis	2.5	3.5	3.9	2.7	2.8
UTI	1.8	4.2	2.9	2.7	2.0
Headache	3.0	2.1	3.2	2.4	3.6
Constipation	1.4	1.6	1.6	1.6	2.0
URI	1.7	2.1	1.5	1.2	0.4
Arthralgia	1.1	1.6	1.3	0.6	0.4
Diarrhea	1.3	1.2	1.5	1.9	1.2
Tachycardia	0.6	1.6	1.2	0.4	0
Abdominal Pain	0.7	1.4	0.6	0.3	0.4
Fatigue	1.0	1.4	1.2	0.8	1.8

The most commonly reported adverse events in the 52-Week, active-controlled study (Study 049) were hypertension, urinary tract infection (UTI), headache, and nasopharyngitis.

Table 9 lists the rates of the most commonly reported adverse events in patients treated with mirabegron for up to 52 weeks in Study 178-CL-049.

Table 9: Percentages of Patients with Adverse Events, Reported by ≥2% of Mirabegron Patients in Study 049

	Mirabegron 50 mg (%)	Mirabegron 100 mg (%)	Tolterodine LA 4 mg (%)
No. of Patients	**812**	**820**	**812**
Hypertension	9.2	9.8	9.6
UTI	5.9	5.5	6.4
Headache	4.1	3.2	2.5
Nasopharyngitis	3.9	4.3	3.1
Back Pain	2.8	3.5	1.6
Constipation	2.8	3.5	2.7
Dry Mouth	2.8	2.3	8.6
Dizziness	2.7	1.6	2.6
Sinusitis	2.7	2.2	1.5
Influenza	2.6	3.0	3.4
Arthralgia	2.1	2.3	2.0
Cystitis	2.1	1.3	2.3

Finally, it should be noted that in the entire development program, several hepatic adverse events were reported. These consisted largely of increases in serum AST and ALT. Of the few hepatic AE cases, almost all were confounded by concomitant drugs or co-morbid conditions. One or two cases were reported in which an increase in serum AST or ALT was accompanied by evidence of a hypersensitivity reaction; however, these rare events were also confounded. Despite the lack of clear attribution to mirabegron, and despite the very small number of reported events, these events will be mentioned in labeling, and the Sponsor will also conduct "enhanced pharmacovigilance" of hepatic adverse events in the postmarketing period.

8.1.3 Special Safety Studies/Other Safety Issues

8.1.3.1 Thorough QT (TQT) Study (178-CL-077)

On January 24, 2012, Joanne Zhang, Janice Brodsky, Jiang Liu, Nitin Mehrotra, Monica Fiszman, and Norman Stockbridge of the Interdisciplinary Review Team – QT (IRT-QT) finalized their consultative report concerning the TQT study conducted for mirabegron. The consultants concluded:

> "*No significant QTc prolongation effect of mirabegron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.*"

The mirabegron TQT study 178-CL-077 was a randomized, blinded, four-treatment-arm parallel-crossover design study, in which 352 healthy subjects received either mirabegron 50 mg, mirabegron 100 mg, mirabegron 200 mg, placebo, or moxifloxacin 400 mg. The overall summary of study results is presented in Table 10.

Table 10: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Mirabegron and the Largest Lower Bound for Moxifloxacin (IRT-QT Analysis)

Treatment	Time (h)	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 time points is 7.6 ms.

The supratherapeutic doses of 100 mg and 200 mg produced C_{max} values 2.9-fold and 8.4-fold greater, respectively, compared to the mean C_{max} for the 50 mg therapeutic dose. The exposures achieved with 200 mg dose are adequate to cover any of the known high clinical exposure scenarios at a dose of 50 mg. The following factors increase exposure to mirabegron: ketoconazole 1.8-fold, severe renal impairment 2.2-fold, and moderate hepatic impairment 1.65-fold. It is notable that mirabegron will be approved with a starting dose of 25 mg, and the dose will be limited to 25 mg in patients with severe renal impairment or moderate hepatic impairment.

The IRT-QT observed a significant relationship between ΔΔQTcI and mirabegron concentrations, but stated that substantial QTc prolongation was not observed in the exposure range of the therapeutic dose of 50 mg.

The difference between males and females is of note. The increase in QT is somewhat greater in females, but in females, the 90% ΔΔQTcI upper bound exceeded 10 ms only for the 200 mg dose level. In females, the mean ΔΔQTcI (90% CI) for 50 mg, 100 mg, and 200 mg were 5.0 ms (3.9, 6.0), 6.3 ms (5.1, 7.5), and 8.8 ms (6.5, 11.1), respectively. The IRT-QT commented as follows:

> *"The mean 90% ΔΔQTcI upper bound exceeded 10 ms only for 200-mg-dose level in females which is consistent with the E14 analysis. However, it is important to note that the exposures achieved with this dose are several fold what is expected with the proposed therapeutic dose of 50 mg."*

The IRT-QT pointed out that in this study, mirabegron increased heart rate on ECG in a dose dependent manner. The maximum mean difference from placebo was 6.7 bpm, 11 bpm, and 17 bpm for 50 mg, 100 mg and 200 mg, respectively. In this study, the increases in heart rate were greater in female subjects compared to males. Finally, in this study, adverse events of headache and palpitations were reported to increase in a dose-related manner.

8.1.3.2 Vision Assessments

The effect of mirabegron on intraocular pressure was assessed in great detail, based upon several adverse event reports of "*increased intraocular pressure*" and "*glaucoma*" in the mirabegron clinical studies. Following receipt of these glaucoma AE reports, extensive discussion ensued between the Sponsor and the Division. The Division enlisted the help of Dr. Wiley Chambers of the Division of Transplant and Ophthalmologic Products (DTOP). In order to address the Division's concerns regarding glaucoma, Astellas used a two-pronged approach:

1) Astellas conducted a systematic evaluation of all glaucoma-type AEs reported in clinical studies within the global mirabegron clinical development program which included 8752 patients (5863 mirabegron-treated patients) and 1000 mirabegron-treated healthy volunteers.
2) Astellas conducted a double-masked, randomized, placebo-controlled, non-inferiority vision study to demonstrate that mirabegron was no different than placebo in its effect on intraocular pressure.

In regard to the glaucoma-type AEs:

Twelve cases were retrieved using the glaucoma SMQ (narrow search) in the mirabegron clinical development program. The external expert panel assessed the cases as follows: 5 cases were classified within the category of glaucoma; 4 of these cases had sufficient documentation to confirm an event of glaucoma:

- 1 patient with acute narrow angle glaucoma
- 1 patient with open angle glaucoma
- 1 patient with glaucoma "suspect"
- 1 patient with chronic narrow angle glaucoma
- 1 patient had insufficient information to confirm or refute glaucoma and was included conservatively as glaucoma

In addition, one case was classified as "non-glaucoma, ocular hypertension" (according to Dr. Chambers, ocular hypertension, by definition, is not glaucoma); and 1 other case as "ocular hypertension". Six (6) patients were classified as not having a treatment emergent adverse event at all, since additional data ascertainment revealed a medical history of a preexisting condition with no evidence of worsening of the underlying condition while on study treatment. Eleven of the 12 retrieved cases were in patients who received mirabegron. The case of chronic narrow angle glaucoma occurred in a patient who received tolterodine.

In regard to the clinical study for ocular safety:

Based on these cases, the Division requested and Sponsor agreed to conduct a randomized, double-masked, placebo-controlled, non-inferiority study to assess the effect of mirabegron on intraocular pressure (IOP). The study used a supratherapeutic dose of mirabegron (100 mg) administered orally once daily for 8 weeks in healthy subjects. The study results, in the Sponsor's opinion, were that 100 mg of mirabegron administered once daily was non-inferior to placebo for the primary endpoint of change from baseline to day 56 in subject average IOP, based on the non-inferiority limit of 1.5 mm Hg. The sponsor concluded that these results and additional eye assessments in other studies, as well as the program-wide evaluation of reported

ocular events, did not suggest an association of mirabegron and glaucoma or other ocular safety issues.

In his final consultative review dated May 10, 2012, Dr. Chambers agreed fully with Sponsor. Dr. Chambers concluded:

- The intraocular pressure clinical study was conducted in accordance with FDA recommendations.
- The Sponsor's interpretation of the study results was accurate. He stated that mirabegron at doses up to 100 mg daily did not appear to raise intraocular pressure.
- The available data did not suggest an association of mirabegron and glaucoma.
- No additional ocular safety issues were noted for mirabegron.

8.1.3.3 Blood Pressure Assessments

Mirabegron was associated with increases in both systolic and diastolic blood pressure and in heart rate in Phase 3 and Phase 1 studies. The increases were smaller in Phase 3 compared to in Phase 1.

In the "pivotal" Phase 3 studies, mirabegron administered at the proposed therapeutic dose of 50 mg once daily was associated with an ***approximately 1 mm Hg*** adjusted mean difference for change from baseline in systolic and diastolic blood pressure (SBP/DBP) compared with placebo.

- The adjusted mean differences versus 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 LA 4 mg were -0.6, 0.7, 0.2 and -0.4 mm Hg for AM measurements, respectively, and -1.0, 0.5, 0.9 and 0.0 mm Hg for PM measurements, respectively.

- The adjusted mean differences versus placebo for change from baseline DBP in the EU/NA OAB 12-week Phase 3 Population were similar to, or smaller than, the changes in SBP.

- In the EU/NA Long-term Controlled population (Study 178-CL-049), the adjusted mean changes from baseline SBP and DBP following mirabegron 50 mg, mirabegron 100 mg and tolterodine were similar. The adjusted mean changes from baseline for SBP in mirabegron 50 and 100 mg and tolterodine groups 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 changes from baseline for DBP were similar to, or smaller than, the changes in SBP.

- The percentages of patients who experienced clinically significant changes in BP were similar between groups, with slightly higher percentages in the mirabegron group in selected categories only.

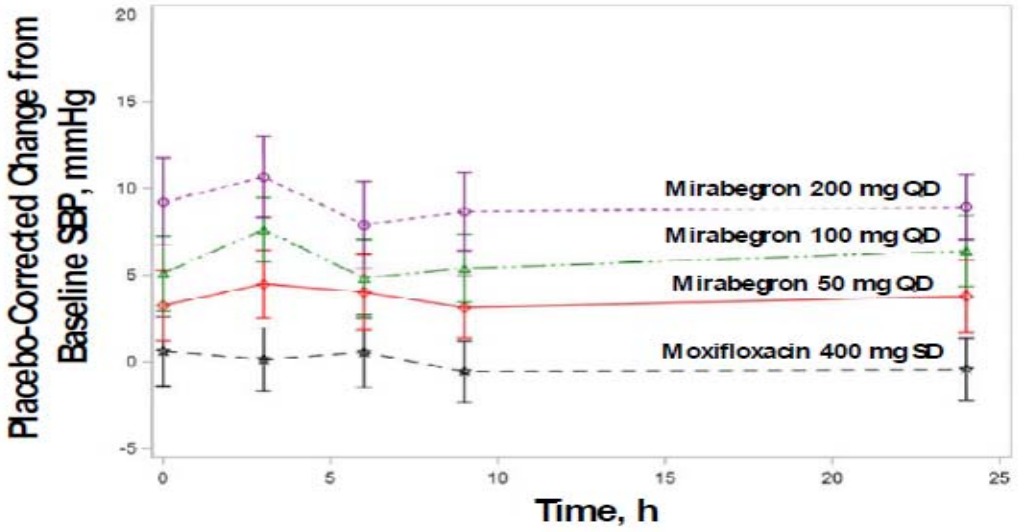
CDTL Comment: *A consultation was obtained from the Division of Cardiovascular and Renal Products (DCRP) to assess the BP data. In their final consultation report dated January 20, 2012, the DCRP consultants (Preston Dunnmon, Thomas Marciniak, and*

Norman Stockbridge) found that the Sponsor's assessment to be accurate. They stated that the Sponsor's Comprehensive Summary of Blood Pressure "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".

Mirabegron was associated with larger increases from baseline in blood pressure in two Phase 1 studies – in Study 178-CL-077, a thorough QT (TQT) study, as well as in Study 178-CL-031, a Phase 1 study exploring the effect of age on pharmacokinetics and tolerability.

- In Study 077, the TQT study in 352 healthy volunteers (mean age 33 years), at hour 3 on the final study day, mean SBP/DBP increases in mirabegron 50 mg subjects compared to placebo subjects were **4.0/1.6 mm Hg**. The 24-hour average increases in SBP from baseline to the final day, as compared to placebo, were 3.0, 5.5, and 9.7 mmHg in the mirabegron 50 mg, mirabegron 100 mg and mirabegron 200 mg dose groups, respectively. Increases in DBP were also dose-dependent, but were smaller than the SBP increases. The increases in SBP are shown in Figure 3:

  Figure 3: Placebo-Corrected, 24-hour, Change from Baseline in Mean Systolic BP – Study 178-CL-077

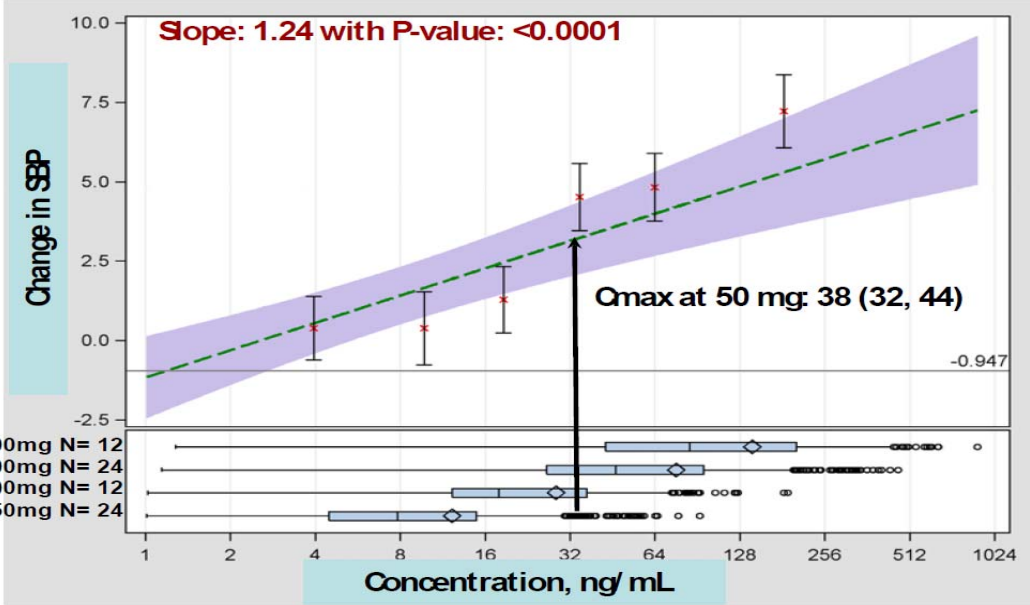


  ***CDTL Comment**: Consultation was obtained from the DCRP co-located Clinical Pharmacology team (Division of Clinical Pharmacology 3 [DCP3]) to evaluate mirabegron blood pressure effects in Studies 178-CL-077 and 178-CL-031 (a multiple dose pharmacokinetic study in young and elderly patients). The 24-hour average increases in Study 077 shown above were confirmed by the team of Rajanikanth Madabushi, Preston Dunnmon and Norman Stockbridge in their final consultation dated June 11, 2012.*

- In Study 178-CL-031 (n=96 healthy volunteers), mirabegron 50 mg demonstrated an increase in mean SBP of approximately **5.5 mmHg** at Hour 4 on the final study day. In this study, following correction for placebo effects, mirabegron overall demonstrated an exposure-dependent increase in blood pressure (for both SBP and DBP) that was

similar in younger (18-55 years) and older (65-77 years) subjects. The maximum blood pressure effects appeared to coincide with the peak mirabegron concentrations. The pharmacokinetic/pharmacodynamic (pK/pD) relationship for SBP is shown in Figure 4 below.

Figure 4: Concentration-Dependent Increase in BP Over Range of Doses in Study 178-CL-031



Notes on the figure: For purposes of this plot, the data were divided into 6 equal bins of observed mirabegron concentrations. The red "x" and associated error bars represent the mean changes in SBP corresponding to the median concentrations for each bin and their corresponding 95% CIs. The dashed green line represents a regression mean for the entire dataset and the purple band is the associated 95% CI.

***CDTL Comment**: Figure 4 was constructed by DCP3 in collaboration with the assistance of the Division of Pharmacometrics in OCP (Jiang Liu and Yaning Wang). The figure represents an analysis of the totality of the pK and BP data from Study 178-CL-031.*

In summary, mirabegron increased blood pressure very modestly in Phase 3 and more in the two Phase 1 studies 077 and 031. The reason for the BP differences observed in Phase 3 and Phase 1 studies remains unclear - there were differences in the patient populations (OAB patients versus healthy volunteers) and in BP testing methodologies. Both sets of BP data will be shown in product labeling and the implications of both sets of BP data have been considered in the FDA safety assessment of mirabegron. A Phase 4 cardiovascular outcomes study has also been required and is expected to inform the clinical significance of the BP findings.

Mirabegron also increased heart rate by a modest amount in the Phase 3 studies and by a larger amount from data obtained from the Phase 1 studies 178-CL-077 and 178-CL-031.

In the EU/NA, 12-Week studies, the placebo-corrected increases in mean heart rate were approximately 0.5 bpm, 1 bpm and 2 bpm for the mirabegron 25 mg, 50 mg and 100 mg groups, respectively, and approximately 2 bpm for the tolterodine LA 4 mg group. The mean heart rate increases in the Long-Term, Active-Controlled Study were similar.

In the Phase 1 studies 178-CL-077 (TQT) and 178-CL-031 (young/elderly), the mirabegron-related increases in heart rate were larger. In Study 077, the mean pulse rate at hour 3 on the final day was increased by 4.3 bpm over placebo for mirabegron 50 mg subjects. In Study 031, the mean pulse rate on hour 4 of the final day was increased over placebo by 2.8 bpm.

8.1.4 Overall Assessment of Safety Findings

The safety data submitted with this NDA exceeds the ICH requirements for a new molecular entity. The reader is referred to section 8.1 of this memo for the numbers of studies conducted, the numbers of patients exposed, and the duration of exposure. Overall, the exposure to mirabegron at the to-be marketed doses (25 mg and 50 mg), and at higher than to-be-marketed doses (100 mg and 200 mg), was extensive and sufficient to define a reasonable picture of the safety of mirabegron. There is also some postmarketing experience from Japan. In sum, appropriate pivotal, long-term and special safety studies have been carried out for this new product.

In assessing the deaths, serious adverse events (SAEs) and discontinuations from adverse events in the mirabegron clinical studies, the numbers of these types of events were few. It is not possible to attribute any of the 11 deaths to mirabegron. SAEs were very few in number and most appeared not to have a relationship to mirabegron. The only SAEs reported in more than 1 patient and at an incidence greater than placebo were *atrial fibrillation* (0.2%) and *prostate cancer* (0.1%). Atrial fibrillation in all SAE cases was confounded by other factors. SAEs of neoplasm were reported at a higher rate in the mirabegron 100 mg group (1.3%) than in the mirabegron 50 mg group (0.1%) or the tolterodine group (0.5%) in the Long-Term, Active-Controlled Study; however, the reported neoplasms were the most common tumors in the target population (e.g., prostate, breast, and lung cancers) and none were reported by more than 2 patients. The clinical significance of this finding in the supratherapeutic dose group is currently unknown, but it will be explored in a required postmarketing study. AEs leading to discontinuations were also few, with only several being reported at a rate greater than placebo (*nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia*). The discontinuation rates due to these events were low; 0.2-0.5%. Reports of hypertension were essentially all from patients with baseline hypertension and were largely variations around a baseline high BP.

The most commonly reported adverse events with mirabegron were hypertension, nasopharyngitis, urinary tract infection, and headache, and these events were reported at only modestly higher rates for mirabegron compared to placebo:

- *Hypertension*: placebo 7.6%, mirabegron 25 mg 11.3%, mirabegron 50 mg 7.5%

- *Nasopharyngitis*: placebo 2.5%, mirabegron 25 mg 3.5%, mirabegron 50 mg 3.9%
- *UTI*: placebo 1.8%, mirabegron 25 mg 4.2%, mirabegron 50 mg 2.9%
- *Headache*: placebo 3.0%, mirabegron 25 mg 2.1%, mirabegron 50 mg 3.2%

It should be noted that in all cases reported as "hypertension", patients had a background baseline condition of hypertension. Most hypertension AEs reflected variations on a hypertensive background.

Other notable adverse events reported at lower rates (generally < 1%) included constipation, diarrhea, abdominal pain, dyspepsia, tachycardia, palpitations, fatigue, URI symptoms, rhinitis, nephrolithiasis, rash, and increased liver function tests.

The commonly reported adverse events reported in the long-term safety study were essentially the same as those reported in the short-term studies with only slightly higher incidences reported in the long-term study.

The Sponsor conducted special safety assessments for vision (intraocular pressure) and for the QT interval and for both these evaluations, evidence was generated in support of the safety of mirabegron. There was no effect of mirabegron on intraocular pressure, and no clinical significant effect on the QT interval. At the supratherapeutic dose of 200 mg, the 90% CI for the placebo-subtracted, change-from baseline in QTcI exceeded 10 msec by a very small amount, and this finding was not considered concerning by IRT-QT.

Mirabegron increased blood pressure very modestly in Phase 3 studies and somewhat more in two Phase 1 studies (178-CL-077 and 178-CL-031). In Phase 3 studies, the increase in SBP associated with mirabegron 50 mg was approximately 1 mm Hg (or slightly lower) with no significant effect on "outliers". In the Phase 1 studies 077 and 031, the placebo-subtracted maximum increases in SBP for mirabegron 50 mg were approximately 4 mm Hg, and 5.5 mmHg, respectively. These two Phase 1 studies did demonstrate an exposure-response relationship for changes in BP. The to-be-marketed dose regimen of 25 mg and 50 mg is expected to further reduce the risk of BP increase. In addition, in order to monitor and further evaluate the clinical significance of the BP finding, the Sponsor will conduct a Phase 4, electronic database epidemiology study to assess cardiovascular outcomes in mirabegron users.

9. Advisory Committee Meeting

On April 5, 2012, the efficacy and safety results from the mirabegron NDA (202,611) were presented before the Reproductive Health Advisory Committee. The FDA's presentation focused on the following areas:

- The mirabegron efficacy results, especially in regard to dose response.
- The overall safety results, with emphasis on selected safety issues:
    - The effect of mirabegron on blood pressure in Phase 3 and Phase 1 studies
    - The increased incidence of neoplasms reported as AEs in the mirabegron 100 mg group in the 52-Week, active-controlled study 178-CL-049.
    - Rare hepatic adverse events reported in clinical trials.
    - Rare hypersensitivity-like events reported in clinical trials.
    - Infrequent urinary tract infections reported in mirabegron subjects in clinical trials.
- General clinical pharmacology issues, such as food effect and effect on CYP2D6 substrates

Both FDA and Sponsor provided detailed meeting background brochures and extensive presentations. The Committee was given time to ask questions, to discuss issues, and to deliberate. Subsequently, the Committee was asked to respond to three questions; the first concerning the efficacy of mirabegron, the second concerning its safety and the last question concerning the overall benefit-risk assessment as it pertains to approval. The following are the Committees' responses to the three questions, abridged from the FDA summary meeting minutes:

1. **(VOTE)** Do the data provide substantial evidence of benefit for mirabegron in the treatment of overactive bladder?

    Yes-8 No-4 Abstain-0

    The committee members largely agreed that the pivotal phase 3 clinical trials met their predefined primary efficacy endpoints by demonstrating a statistically significant decrease in the number of incontinence episodes and micturitions in a 24 hour period compared to baseline. There were recommendations from some panel members to consider the 25 mg dose because it appeared to represent the lowest effective dose.

2. **(VOTE)** Has adequate safety been demonstrated for mirabegron in the treatment of overactive bladder?

    Yes-9 No-3 Abstain-0

    The majority of the committee members agreed that the side effects had been examined well and that mirabegron was generally safe. There were concerns voiced regarding some of the safety issues, for example, the blood pressure increases reported in clinical studies. Some members also voiced concerns regarding the liver and neoplastic AEs. The Committee encouraged the FDA to require postmarketing studies to further delineate the clinical significance of the potential risks.

3. **(VOTE)** Considering all the available data, including information from the briefing documents and today's discussion, does the overall benefit-risk assessment support approval of mirabegron for the treatment of overactive bladder?

   Yes-7 No- 4 Abstain-1

   The majority of the committee members agreed that the overall benefit-risk assessment supported approval because the predefined primary efficacy objectives had been achieved and the product appeared generally safe. Several members discussed consideration of the 25 mg dose. Panel members recommended that the applicant conduct postmarketing surveillance efforts and postmarketing studies, including the following objectives:
   - To evaluate which users have greatest potential benefit
   - To further clarify the overall clinical benefit and effects on quality of life
   - To clarify the risks of cancer and cardiovascular disease
   - To monitor reports of cancer, cardiovascular disease, hepatic injury, hypersensitivity reactions, and urologic adverse events in the post-marketing period.

The Advisory Committee's comments and recommendations were taken into consideration during the NDA review.

10. Pediatrics

The Sponsor requested a partial waiver of pediatric studies in patients from birth through 4-years and a deferral in patients 5-17 years. At a May 30, 2012, meeting of Pediatric Review Committee (PeRC), the Division expressed support for the Sponsor's plan. During the meeting, the PeRC agreed with the Division and expressed support for the Sponsor's plan.

On June 13, 2012, in an eMAIL from George Greeley of the Pediatric and Maternal Health Staff, DRUP was notified that the PeRC agreed to grant the partial waiver and deferral. The eMAIL stated:

"*This email serves as confirmation of the review for the mirabegron (YM178) product conducted by the PeRC PREA Subcommittee on May 30, 2012.*

The Division presented a partial waiver in patients birth through 4 years because studies are impossible or highly impracticable because overactive bladder is not a condition in infants or young children, and a deferral in patients 5-17 years until additional safety or efficacy data have been collected. Mirabegron is being studied for the treatment of overactive bladder.

The waiver is being requested because overactive bladder is not a condition in infants or young children 0 to 4 years and 11 months who are not yet bladder trained. While the Sponsor's proposed pediatric plan appears reasonable, we advise that human studies among subjects 5 to 17 years and 11 months should be deferred. There are nonclinical and clinical reasons for deferring studies in pediatric patients older than 5 years. First, appropriate animal studies have not yet been performed. An area of nonclinical concern is

a potential effect on bone maturation. Second, the main clinical areas of concern are the effect of mirabegron on increasing blood pressure and a potential effect on new malignant events in adult. Both these clinical concerns will be addressed in required postmarketing adult studies to inform future pediatric studies.

In addition, DRUP is awaiting submission of the full juvenile animal protocol. DRUP agrees with the nonclinical pediatric study proposal as outlined, but recommends that the sponsor include a measurement of bone growth at necropsy such as tibial length, if it is not included in the protocol.

The PeRC agreed with the Division to grant a partial waiver in patients (from) birth through 4 years and to the deferral in patients 5 through 17 years of age."

11. Other Relevant Regulatory Issues

Division of Drug Advertising, Marketing and Communication (DDMAC)

In their final consult report dated June 13, 2012, Jessica Cleck Derenick and Jina Kwak provided a total of 20 comments on various sections of the label, including Highlights, Dosage and Administration (D &A), Warnings & Precautions, Adverse Reactions, Drug Interactions, Clinical Pharmacology, Clinical Studies and Patient Counseling.

All the DDMAC comments and recommendations were carefully considered. Some were addressed through internal discussions amongst the primary review team and through labeling revision and successful negotiations with Sponsor (e.g. changes to the Effect on Electrophysiology section). Some DDMAC recommendations were not taken, but these were either relatively minor edits (e.g., change "events" to "reactions", or suggestions for which the team decided there was sufficient justification to keep the label as is.

Office of Scientific Investigation (OSI)

At the request of DRUP, OSI audited three clinical investigative sites: Dr. William Koltan (San Diego, CA), Dr. Evan Goldfisher (Poughkeepsie, NY) and Dr. Kjetil Hoye (Hamar, Norway). Dr. Koltan enrolled 29 subjects and 50 subjects in Studies 047 and 074, respectively. Dr. Goldfisher enrolled 29 subjects in Study 047. Dr. Hamar enrolled 50 subjects and 46 subjects in Studies 046 and 074, respectively. These three investigational sites were selected for inspection because of their relatively large enrollment and significant primary efficacy results pertinent to decision-making.

In addition to these three clinical investigative sites, the Sponsor was also inspected for administrative record-keeping, adverse event reporting, CRF handling, etc.

No regulatory violations were detected at Dr. Goldfisher's site or at Dr. Hoye's site and a Form FDA 483 was not issued to either of those investigators. Dr. Koltan was issued a Form FDA 483, but the regulatory violations observed at Dr. Koltan's site were minor in nature relative to the robust study designs and large sample sizes. For example, among other minor violations, two subjects did not record their blood pressure and pulse rates in the six days prior to visit 2, one male subject was identified under multiple study numbers, one subject enrolled

despite previous use of the test article, and one subject did not have a protocol-specified ECG at Visit 5.

In regard to the Sponsor site inspection, a Form FDA 483 was issued at the conclusion of the inspection. The deficiencies listed for the Astellas site were minor, and included items such as: lack of a signed Statement of Investigator Form FDA 1572 from Dr. Kjetil Hoye; 12 subjects in Protocol 178-CL-074 received prohibited concomitant medications; nine subjects in Protocol 178-CL-074 were randomized to two mirabegron studies; one subject in Protocol 178-CL-047 was enrolled though not practicing a highly reliable form of birth control; one subject at Site #3225 in Protocol 178-CL-046 and two subjects at Site #1617 in Protocol 178-CL-047 were enrolled despite an average daily urine output that met exclusion criteria.

Overall, OSI concluded: "*Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication*".

Financial Disclosure

Financial disclosure documents were submitted for principal and sub-investigators for clinical studies for the four Phase 3 studies (178-Cl-046, -047, -074, and -049). A total of 189, 128, 147 and 306 investigators in Studies 046, 047, 074 and 049, respectively, provided disclosures and only 1 had relevant financial disclosure information to declare. (b) (6), an investigator in Studies 047 and 049 indicated receiving payments of other sorts (honoraria) from Astellas as related to a national consulting role in regards to the drug VESIcare. Based on the very large number of investigators in the 4 pivotal studies, and (b) (6) having received honoraria for a different drug, this single case was not considered to affect the outcomes of the mirabegron efficacy and safety studies.

Office of Medical Policy Initiatives/ Division of Medical Policy Programs (DMPP)

On June 8, 2012, Sharon Williams, Melissa Hulett and LaShawn Griffiths of DMPP provided a final consult regarding the Sponsor's proposed Patient Package Insert (PPI). DMPP concluded:

> "*The PPI is acceptable with our recommended changes.*"

DMPP pointed out that in conducting their review of the PPI they based their edits on the June 6, 2012, FDA-revised draft substantially complete PI (SCPI), and took into consideration the approved VESIcare (comparator) labeling dated January 17, 2012.

DMPP provided a number of edits to the PPI, most of which were intended to update the document to be consistent with current standards of PPI formatting and terminology (e.g., proper order of sections, proper font size and type, add the manufacturer's website and phone number, etc), and to make the PPI consistent with the PI (e.g., add information from Warnings & Precautions and from Adverse Reactions).

All edits to the original PPI were conveyed to Sponsor, and all were ultimately agreed upon by Sponsor.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

Container/Carton/Package Insert Labeling

On May 31, 2012, Manizeh Siahpoushan and Zachary Oleszczuk from DMEPA provided a final review of the Sponsor-revised mirabegron carton and container labeling. DMEPA's review of these materials was intended to evaluate the Sponsor's final revisions based upon the recommendations provided in the DMEPA reviews dated November 8, 2011, March 19, 2012 and May 15, 2012. DMEPA concluded:

> "*The revised container labels and carton labeling address all of DMEPA's concerns. Thus, we find the revised container labels and carton labeling acceptable and have no additional comments to the Applicant at this time.*"

In the DMEPA review dated May 15, 2012, the Sponsor was reminded to increase the prominence of several key messages, including:

- Take once- daily
- Swallow tablet whole. Do no cut, crush, or chew tablet

The final labeling clearly demarcates these specific messages.

In the DMEPA review dated March 19, 2012, the Sponsor was reminded of the following

- Reduce the prominence of the 'Rx Only' statement
- Reduce duplication of the product strengths
- Relocate the quantity statement to reduce crowding.

The final labeling includes these specific revisions.

Finally, in the DMEPA review dated November 8, 2011, the Sponsor was told:

- Improve differentiation of the two doses by reducing overlapping colors and employing more color differentiation
- Improve the prominence of the trade and proprietary names and decrease prominence of the strength, the graphic, the Rx Only statement, and the company logo.
- Include on the carton and container labels that the product is to be swallowed whole and not chewed, divided or crushed.

The final labeling includes these specific revisions.

Trade name

On June 11, 2012, in their final tradename review, Manizeh Siahpoushan, Zachary Oleszczuk and Carol Holquist of the Division of Medication Errors Prevention and Analysis (DMEPA), stated:

> "*We have completed our review of the proposed proprietary name,* ***Myrbetriq****, and have concluded that this name is acceptable.*
>
> *The proposed proprietary name is acceptable from both a promotional and safety perspective.*"

During the course of this NDA review, DMEPA was asked to conduct proprietary name reviews for 4 other proposals: (b) (4) All of these potential trade names were rejected by DMEPA. The reasons for these DMEPA decisions are provided herein:

- The proposed proprietary name (b) (4) was found unacceptable in OSE Review #2009-1305, dated December 8, 2009, due to likelihood of name confusion with (b) (4)

- The proposed proprietary name (b) (4) was found unacceptable in OSE Review #2010-436, dated August 10, 2010, due to likelihood of name confusion with (b) (4) and again in OSE Review #2011-238, dated July 15, 2011 (request for reconsideration (b) (4)

- The proposed proprietary name (b) (4) was found unacceptable in OSE Review #2011-3947, dated December 16, 2011, due to likelihood of name confusion with (b) (4)

- The proposed proprietary name (b) (4) was found unacceptable due to orthographic similarity and shared product characteristics with the marketed product, (b) (4)

On June 18, 2012, in a final DMEPA memo, Manizeh Siahpoushan and Zachary Oleszczuk, stated that the Sponsor request for change in pronunciation of the proprosed trade name Myrbetriq from "meer-beh-trick" to "meer-beh-treek" was re-evaluated and was found to be acceptable. DMEPA stated:

> "*The re-evaluation of the proposed proprietary name, Myrbetriq, did not identify any vulnerabilities that would result in medication errors considering we evaluated this name with multiple pronunciations during our previous review*."

Office of Compliance

On April 19, 2012, the Office of Compliance provided an "Acceptable" recommendation via EES for the facilities involved in the NDA.

12. Labeling

Labeling discussions have proceeded as per standard practice. The key labeling issues were: 1) description of the effect of mirabegron on blood pressure, 2) description of the effect of mirabegron on CYP2D6 substrates (such as desipramine and metoprolol), and 3) description of mirabegron adverse reactions and other serious adverse events observed in the clinical studies (e.g., serious adverse events in the Neoplasm category). As of June 21, 2012, labeling negotiations were proceeding well.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this new drug application be Approved.

13.2 Risk Benefit Assessment

Efficacy
In three, randomized, double-blind, 12-week, placebo-controlled studies, mirabegron 50 mg demonstrated efficacy in the treatment of OAB, as demonstrated by success on the co-primary endpoints (change from baseline in number of micturitions [in all subjects], and change ferom baseline in number of incontinence episodes [in subjects with incontinence at baseline]), as well as success in most secondary endpoints. In Study 178-CL-074, mirabegron 25 mg also demonstrated efficacy for the treatment of OAB. The treatment effect for both doses is highly statistically significant compared to placebo and based on all the efficacy data, the effect is considered to be clinically meaningful in the treatment of OAB.

In regard to dose selection, the data demonstrates benefit for both doses at Week 4, and similar primary efficacy results for mirabegron 25 mg and 50 mg at Week 8, but secondary endpoints provide evidence for greater overall clinical benefit for mirabegron 50 mg compared to 25 mg. Therefore, in order to optimize the benefit/risk ratio, a starting dose of 25 mg for all patients, followed by an increase to mirabegron 50 mg based on individual patient efficacy and tolerability is considered reasonable and appropriate. It may take up to 8 weeks to achieve optimal results with mirabegron 25 mg.

Safety
Appropriate pivotal (Phase 3), long-term and special safety studies have been carried out for this new product. The extent of the patient exposure to mirabegron in clinical trials is extensive. It is not possible to attribute any death to mirabegron. The only SAEs reported in more than 1 patient and at an incidence greater than placebo were atrial fibrillation (0.2%) and prostate cancer (0.1%), and the atrial fibrillation cases was confounded by other factors. SAEs of neoplasm were reported at a higher rate in the mirabegron 100 mg group (1.3%) than in the mirabegron 50 mg group (0.1%) or the tolterodine group (0.5%) in the Long-Term, Active-Controlled Study; however, the reported neoplasms were the most common tumors in the target population (e.g., prostate, breast, and lung cancers) and none were reported by more than 2 patients. The clinical significance of this finding in the supratherapeutic dose group is currently unknown, but it will be explored in a required postmarketing electronic database epidemiology 4 study.

AEs leading to discontinuations were also few, with rates of approximately 0.2%, and only several (nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia) were reported at a rate greater than placebo. Notably, reports of hypertension were essentially all from patients with baseline hypertension and were largely variations around a baseline high BP. The most commonly reported adverse reactions to mirabegron were hypertension, nasopharyngitis, urinary tract infection, and headache, and these were reported at only

modestly higher rates for mirabegron compared to placebo. Again, it is notable that in all cases reported as "hypertension", patients had a background baseline condition of hypertension. Other notable adverse events reported at lower rates (generally < 1%) included gastrointestinal symptoms (constipation, diarrhea, abdominal pain, dyspepsia), upper respiratory symptoms (URI-like symptoms, rhinitis), cardiovascular symptoms (tachycardia, palpitations, fatigue), other urologic events (nephrolithiasis), and rarely, rash and increased liver function tests. The long-term study revealed a similar profile of adverse reactions and long-term reporting rates for these events were only modestly increased over short-term rates.

The Sponsor conducted special safety assessments for vision (intraocular pressure) and for the QT interval. There was no effect of mirabegron on intraocular pressure, and no clinically significant effect on the QT interval. Finally, mirabegron did increase heart rate and blood pressure modestly in Phase 3 studies and somewhat more in two Phase 1 studies (178-CL-077 and 178-CL-031). In the Phase 3 studies, the increase in systolic BP associated with mirabegron 50 mg was approximately 1 mm Hg (or slightly lower). In the Phase 1 studies 077 and 031, the placebo-subtracted maximum increases in SBP for mirabegron 50 mg were approximately 4 mm Hg, and 5.5 mmHg, respectively. These two Phase 1 studies did demonstrate an exposure-response relationship for changes in BP. In order to reduce the potential risk associated with the BP increase, a starting dose of 25 mg with increase to 50 mg as needed and as tolerated was proposed, and was acceptable to Sponsor. In addition, the Sponsor will conduct a Phase 4, electronic database epidemiology study to assess cardiovascular outcomes in mirabegron users.

Therefore, the Sponsor has agreed to conduct two Phase 4 safety studies as postmarketing requirements and in addition, has agree to monitor for hepatic adverse events using an enhanced pharmacovigilance strategy.

Overall, then, there are no unresolved efficacy or safety issues for this application and the risk/benefit ratio is considered acceptable for marketing approval.

13.3 Recommendation for Postmarketing Risk Management Activities

The Division requested and the Sponsor agreed to implement methods of enhanced pharmacovigilance for evaluation of possible drug-induced liver injury in the postmarketing setting through evaluation of reported hepatic adverse events. Other than this stipulation, there are no specific recommendations for postmarketing risk management activities.

13.4 Recommendation for other Postmarketing Study Commitments

The Division requested, and the Sponsor agreed to conduct two (2) postmarketing clinical studies, both as postmarketing requirements (PMR). These studies will be:

1) **PMR #1** A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron). The purpose of this study

is to investigate the clinical significance, in terms of occurrence of serious cardiovascular events, of the increases in blood pressure observed in clinical trials.

2) **PMR #2**: A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron).

   The purpose of this study is to investigate the effect of mirabegron on new malignant events based upon the finding of an increased incidence of neoplasms in the mirabegron 100 mg group compared to the mirabegron 50 mg or tolterodine groups, observed in the long-term, active-controlled study 178-CL-049.

The Sponsor was made aware by teleconference on June 21, 2012 (and in writing on the same day), that if either of these post-marketing epidemiologic safety studies are not successful, an interview or survey-based, prospective cohort study of the safety signal would follow. The Sponsor was provided with an FDA-proposed outline for such a prospective study in the event it becomes necessary.

13.5 Recommended Comments to Applicant

There are no additional comments for Sponsor at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S HIRSCH
06/26/2012

AUDREY L GASSMAN
06/26/2012