

Report on the Deliberation Results

June 3, 2011

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Betanis Tablets 25 mg Betanis Tablets 50 mg
[Non-proprietary name]	Mirabegron (JAN*)
[Applicant]	Astellas Pharma Inc.
[Date of application]	June 18, 2010

[Results of deliberation]

In the meeting held on June 1, 2011, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The products are not classified as biological products or specified biological products, and the re-examination period is 8 years. The drug substance is classified as a poisonous drug, and the drug product is classified as a powerful drug.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

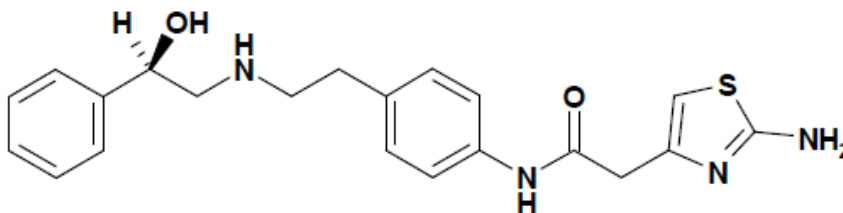
Review Report

May 12, 2011
Pharmaceutical and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Betanis Tablets 25 mg Betanis Tablets 50 mg
[Non-proprietary name]	Mirabegron
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	June 18, 2010
[Dosage form/Strength]	A film-coated tablet containing 25 mg or 50 mg of mirabegron
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]
Structural formula:



Molecular formula:	C ₂₁ H ₂₄ N ₄ O ₂ S
Molecular weight:	396.51
Chemical name:	2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-[(2R)-2-hydroxy-2-phenylethyl]amino)ethyl]phenyl]acetamide
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Results

May 12, 2011

[Brand name]	Betanis Tablets 25 mg Betanis Tablets 50 mg
[Non-proprietary name]	Mirabegron
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	June 18, 2010
[Results of review]	

Based on the submitted data, the efficacy of the product in patients with overactive bladder has been demonstrated. The safety of the product is acceptable in view of its observed benefits as long as appropriate precautions are provided for proper use. However, it should not be disregarded that the non-clinical and clinical pharmacology studies have indicated a cardiovascular risk and effects on the eyes and reproductive organs. It is thus necessary to take measures such as advising caution and providing information for ensuring the safety of patients treated with mirabegron. In addition, given that the product involves a new mechanism of action, and that in clinical practice, the product is expected to be used in combination with approved anticholinergics, drugs for overactive bladder, it is necessary to investigate the efficacy and safety of the concomitant use of mirabegron with anticholinergics by additionally conducting a post-marketing clinical study. It is also necessary to collect the following information via post-marketing surveillance: adverse events related to QT prolonged and Torsades de Pointes (TdP), occurrence of glaucoma, safety of the concomitant use of α_1 receptor antagonist with mirabegron in patients with benign prostatic hyperplasia accompanied by overactive bladder, and effects on glucose metabolism.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication, dosage and administration.

[Indication]	Urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder
[Dosage and administration]	The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal.

Review Report (1)

February 25, 2011

I. Product Submitted for Registration

[Brand name]	Betanis Tablets 25 mg Betanis Tablets 50 mg
[Non-proprietary name]	Mirabegron
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	June 18, 2010
[Dosage form/Strength]	A film-coated tablet containing 25 or 50 mg of mirabegron
[Proposed indication]	Urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder
[Proposed dosage and administration]	The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal. The dose may be adjusted according to the patient's age and symptoms up to 100 mg per day.

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Mirabegron is a selective β_3 -adrenoceptor agonist discovered by Astellas Pharma Inc. The function of the lower urinary tract, the pathway from the bladder to the external urethral orifice, is urine storage and urination, which are mainly modulated by 3 nervous systems: the sympathetic, parasympathetic, and somatic nervous systems. During the urine storage phase in which generated urine is pooled in the bladder, the sympathetic nervous system mainly governs the bladder and noradrenaline released from the hypogastric nerve ending stimulates β -adrenoceptors present in the bladder smooth muscle, thereby relaxing the bladder (*Urology*. 2002;59(Suppl 1):25-9, *Acta Pharmacol Toxicol*. 1977;40:14-21). At present, it is recognized that β_3 -adrenoceptors are mainly responsible for the relaxation response of the human bladder smooth muscle mediated by activation of the sympathetic nerves (*Urology*. 2002;59(Suppl 1):25-9, *Br J Pharmacol*. 1998;124:593-9, *J Pharmacol Exp Ther*. 1999;288:1367-73). Mirabegron is expected to alleviate symptoms of overactive bladder (OAB) such as urinary frequency, urgency, and urge urinary incontinence by exerting a relaxant effect on bladder smooth muscle through β_3 -adrenoceptors.

In Japan, the marketing application for mirabegron indicated for the treatment of OAB has been filed based on the results from Japanese clinical studies. As of February 2011, mirabegron has not been approved in any country or region including Japan. Foreign phase III and long-term treatment studies have been completed in the US and European countries (the UK, Germany, France, etc.), while in Asian countries (Korea, China, Taiwan, etc.), a phase III study is ongoing. Since glaucoma was reported in the foreign long-term treatment study, a clinical study is ongoing in the US to investigate the effect on the intraocular pressure in accordance with the request of the US Food and Drug Administration (FDA).

2. Data relating to quality

2.A. *Summary of the submitted data*

The proposed product comprises film-coated tablets containing 25 or 50 mg of mirabegron (molecular formula, $C_{21}H_{24}N_4O_2S$; molecular weight, 396.51).

2.A.(1) Drug substance

2.A.(1).1 Characterization

a. Structure

Mirabegron has one chiral center in its chemical structure, and the asymmetric carbon has the *R* configuration. The chemical structure has been elucidated by elemental analysis, mass spectrometry, hydrogen nuclear magnetic resonance spectrometry (1H -NMR), carbon nuclear magnetic resonance spectrometry, ultraviolet-visible spectrophotometry (UV), infrared spectrophotometry (IR), and single-crystal X-ray crystallography.

b. General properties

As the general properties of the drug substance, description, melting point, pH, dissociation constant (pKa), optical rotation, distribution coefficient, solubility, hygroscopicity, thermal analysis, crystallinity, crystalline polymorphism, and particle size have been determined.

Mirabegron is freely soluble in dimethylsulfoxide, soluble in methanol, sparingly soluble in ethanol (99.5), slightly soluble in acetonitrile, and practically insoluble in water. It is sparingly soluble or slightly soluble in solutions at pH 1.0 to 7.0, very slightly soluble in those at pH 7.5 and pH 9.0, and practically insoluble in those at pH 11.0 and pH 13.0.

The particle sizes at cumulative 10%, 50%, and 90% were found to be μm , μm , and μm , respectively.

2.A.(1).2 Manufacturing process

The manufacturing process for the drug substance consists of the following 6 steps.

Step 1 (reaction process)

Step 2 (reaction process)

[REDACTED]

Step 3 (reaction and purification processes)

[REDACTED]

The reaction mixture was filtered, and then concentrated under reduced pressure.

[REDACTED]

[REDACTED]

Step 4 (reaction process)

[REDACTED]

Step 5 (purification process)

[REDACTED]

The mixture was cooled by stirring to form the crystals of mirabegron and filtered, and the crystals on the filter were used as the drug substance.

Step 6 (packaging, labeling, and storage processes, testing)

The drug substance obtained in Step 5 was placed in double-layered polyethylene bags, the bags were filled in a fiber drum and stored.

The manufacturing process of the drug substance was subjected to risk assessment and risk control.

[REDACTED]

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance consist of description (appearance), identification (UV, IR), purity (heavy metals [color identification test], related substances [high performance liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)]),

water content (coulometric titration), residue on ignition (residue on ignition test), microbial limits (microbial limit test), and assay (HPLC).

2.A.(1).4) Stability of drug substance

As stability studies of the drug substance, the following studies were conducted using lots manufactured at a commercial scale.

- [1] Long-term testing (25°C/60%RH, double-layered polyethylene bags/fiber drum, 24 months)
- [2] Accelerated testing (40°C/75%RH, double-layered polyethylene bags/fiber drum, 6 months)
- [3] [REDACTED]
- [4] [REDACTED]
- [5] [REDACTED]

[REDACTED]

In the long-term testing ([1]), accelerated testing ([2]), and stress testing ([3], [4]), no changes were observed over time in any of the attributes tested. [REDACTED].

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in accordance with “Guideline on Evaluation for Stability Data” (PFSB/ELD Notification No. 0603004, dated June 3, 2003). The long-term testing is planned to be continued up to [REDACTED] months of storage.

2.A.(2) Reference standards or materials

The proposed specifications for the standard material consist of description (appearance), identification (UV, IR, ¹H-NMR), purity (related substances [HPLC], residual solvents [GC]), water content (coulometric titration), residue on ignition (residue on ignition test), and assay (mass balance).

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product

[REDACTED]

2.A.(3).2) Formulation development

[REDACTED]

[REDACTED]

2.A.(3).3) Manufacturing process

The manufacturing process for the drug product consists of the following 6 steps.

Step 1 ([REDACTED])

[REDACTED]

Step 2 ([REDACTED])

[REDACTED]

Step 3 ([REDACTED])

[REDACTED].

Step 4 ([REDACTED])

[REDACTED]

Step 5 ([REDACTED])

Method 1 (PTP/pillow package [with a desiccant]):

[REDACTED]

Method 2 (bottle [with a desiccant]):

[REDACTED]

Step 6 (Packaging, labeling, storage, testing processes)

The PTP/pillow (with a desiccant) packages and bottle (with a desiccant) packages were packed, labeled, and stored.

[REDACTED]

2.A.(3).4) Control of drug product

The proposed specifications for the drug product consist of description (appearance), identification (UV), purity (related substances [HPLC]), content uniformity (UV), dissolution (HPLC), water content (volumetric titration), and assay (HPLC).

2.A.(3).5) Stability of drug product

As stability studies of the drug product, the following studies were conducted using lots manufactured at a commercial scale.

- [1] Long-term testing ($25 \pm 2^{\circ}\text{C}/60 \pm 5\%\text{RH}$, PTP/pillow [with a desiccant], 24 months)
- [2] Long-term testing ($25 \pm 2^{\circ}\text{C}/60 \pm 5\%\text{RH}$, bottle [with a desiccant], 24 months)
- [3] Accelerated testing ($40 \pm 2^{\circ}\text{C}/75 \pm 5\%\text{RH}$, PTP/pillow [with a desiccant], 6 months)
- [4] Accelerated testing ($40 \pm 2^{\circ}\text{C}/75 \pm 5\%\text{RH}$, bottle [with a desiccant], 6 months)
- [5] Stress testing, stability to temperature ($^{\circ}\text{C}$, PTP/pillow [with a desiccant], 3 months)
- [6] [REDACTED]
- [7] [REDACTED]
- [8] Stress testing, photostability (D_{65} light source; an overall illumination of [REDACTED] lx·h [25 mg tablets], [REDACTED] lx·h [50 mg tablets]; an integrated near ultraviolet energy of [REDACTED] W·h/m² [25 mg tablets], [REDACTED] W·h/m² [50 mg tablets]; petri dish [control, dish/aluminum foil, protected from light], 50 days)

In the long-term testing ([1], [2]), samples were tested for description, related substances, BHT, dissolution, hardness, water content, and content at 0, 3, 6, 9, 12, 18, and 24 months, and the microbial limit was measured at 0, 12, 18, and 24 months. Samples were tested for description, related substances, BHT, dissolution, hardness, water content, and content at 0, 1, 3, and 6 months in the accelerated testing ([3], [4]), at 0, 1, and 3 months in the stress testing ([5], [6], [7]), and at 0, 25, and 50 days in the stress testing ([8]).

In the long-term testing ([1]), no changes over time were observed in any attribute tested. In the long-term testing ([2]), a decrease in BHT and an increase in water content were noted.

[REDACTED]

Based on the above, the changes observed over time in the long-term testing (24 months) and accelerated testing fell within the specifications, a shelf life of 36 months has been proposed for the drug product when stored in a PTP/pillow (with a desiccant) package and bottle (with a desiccant) package at room temperature in accordance with “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004, dated June 3, 2003). The study data at 36 months from the ongoing long-term testing will be evaluated when it becomes available, and the shelf life will be reviewed, where necessary.

2.B. Outline of the review by PMDA

2.B.(1) Shelf life for the drug product

In the long-term testing in a bottle (with a desiccant) package, the measured water content was increased with time and reached [REDACTED]% in the 25 mg tablets and [REDACTED]% in the 50 mg tablets at 24 months, compared to the acceptance criterion of \leq [REDACTED]%. Since the measured water content may exceed the upper specification limit ([REDACTED]%) at 36 months, if the shelf life is set as proposed by the applicant. Thus, PMDA asked the applicant to explain this matter using the statistical analysis results.

The applicant explained as follows:

Regression analysis was performed using data at 24 months from the long-term testing for the

PMDA has concluded that the proposed shelf life of 36 months for the drug product is acceptable at present, because the applicant's explanation that the estimated water content at 36 months conforms to the specification is appropriate according to the regression analysis results, which show that the upper limit of a one-sided 95% CI of the population mean does not exceed the upper specification limit of the water content.

Since the specifications of PEO1 have been identified in accordance with the Japanese Pharmacopoeia, PMDA has concluded, based on the submitted data, that there are no particular problems with the specifications, and that there are no particular problems with the stability of this new excipient.

Based on the submitted data, PMDA has concluded that the recommended clinical dose and dosage regimen for the proposed product are unlikely to cause safety concerns attributable to PEO1, and therefore use of PEO1 in the proposed product is acceptable.

3. Non-clinical data

3.(i).A. Summary of the submitted data

3.(i).A.(1).1 Agonistic effect on β -adrenoceptors and specificity

Chinese hamster ovary cells (CHO cells) expressing each subtype of β -adrenoceptors (β_1 , β_2 , β_3) of human and various animals were used to investigate agonistic effects of mirabegron and isoproterenol, nonselective β -adrenoceptor agonist, on each subtype of β -adrenoceptors, based on the intracellular cAMP concentration.

In the cells expressing human β_3 -adrenoceptors, mirabegron (0.01-10,000 nM) increased the intracellular cAMP concentration in a concentration-dependent manner. The 50% effective concentration (EC₅₀) of mirabegron was 1.5 nM, taking the maximum response to isoproterenol,

a full agonist, as 100% and the relative maximum activity of mirabegron (intrinsic activity) was 0.8 when the maximum response to isoproterenol was taken as 1. In contrast, in the cells expressing human β_1 - and β_2 -adrenoceptors, the intrinsic activity of mirabegron was 0.1 and 0.2, respectively, and the concentration of both receptors did not reach EC_{50} in the concentration range tested (0.01-10,000 nM). Isoproterenol (0.01-10,000 nM) increased the intracellular cAMP concentration in the cells expressing human β_1 -, β_2 -, and β_3 -adrenoceptors in a concentration-dependent manner, with EC_{50} values being 34, 21, and 49 nM, respectively.

ii) Cells expressing rat β -adrenoceptors (Attached document 4.2.1.1-2)

In the cells expressing rat β_3 -adrenoceptors, mirabegron (1-10,000 nM) increased the intracellular cAMP concentration in a concentration-dependent manner, and the EC_{50} and intrinsic activity were 19 nM and 1.0, respectively. Even in the cells expressing rat β_1 -adrenoceptors, mirabegron (1-10,000 nM) increased the intracellular cAMP concentration in a concentration-dependent manner, and the EC_{50} and intrinsic activity were 610 nM and 0.6, respectively. In contrast, the intrinsic activity of mirabegron in the cells expressing rat β_2 -adrenoceptors was 0.1, and the concentration did not reach EC_{50} in the concentration range tested (1-10,000 nM). Isoproterenol (1-10,000 nM) increased the intracellular cAMP concentration in the cells expressing rat β_1 -, β_2 -, and β_3 -adrenoceptors in a concentration-dependent manner, with EC_{50} values being 31, 110, and 60 nM, respectively.

iii) Cells expressing dog β -adrenoceptors (Attached document 4.2.1.1-3)

In the cells expressing dog β_3 -adrenoceptors, mirabegron (0.01-10,000 nM) increased the intracellular cAMP concentration in a concentration-dependent manner, and the EC_{50} and intrinsic activity were 7.9 nM and 0.8, respectively. In contrast, in the cells expressing dog β_1 - and β_2 -adrenoceptors, the intrinsic activity of mirabegron was 0.3 and 0.1, respectively, and neither receptor achieved EC_{50} in the concentration range tested (0.01-10,000 nM). Isoproterenol (0.01-10,000 nM) increased the intracellular cAMP concentration in the cells expressing dog β_1 -, β_2 -, and β_3 -adrenoceptors in a concentration-dependent manner, with EC_{50} values being 80, 39, and 180 nM, respectively.

iv) Cells expressing cynomolgus monkey β -adrenoceptors (Attached document 4.2.1.1-4)

In the cells expressing cynomolgus monkey β_3 -adrenoceptors, mirabegron (1-10,000 nM) increased the intracellular cAMP concentration in a concentration-dependent manner, and the EC_{50} and intrinsic activity were 32 nM and 0.8, respectively. In contrast, in the cells expressing cynomolgus monkey β_1 - and β_2 -adrenoceptors, the intrinsic activity of mirabegron was 0.2 and 0.1, respectively, and neither receptor achieved EC_{50} in the concentration range tested (1-10,000 nM). Isoproterenol (1-10,000 nM) increased the intracellular cAMP concentration in the cells expressing cynomolgus monkey β_1 -, β_2 -, and β_3 -adrenoceptors in a concentration-dependent manner, with EC_{50} values being 84, 77, and 170 nM, respectively.

(b) Affinity for human β -adrenoceptors (Attached document 4.2.1.1-5 [Reference data])

A receptor binding study was conducted using a membrane fraction of the cells expressing each subtype (β_1 , β_2 , β_3) of human β -adrenoceptors and radioisotope ligand for the corresponding subtype to investigate the affinity of mirabegron for each subtype. As a result, mirabegron (300-100,000 nM, 100-30,000 nM, and 3-30,000 nM in β_1 , β_2 , and β_3 experimental systems, respectively) inhibited binding of the radioisotope ligand to the corresponding subtype, and dissociation constants (K_i) indicating the affinity of mirabegron for human β_1 -, β_2 -, and β_3 -adrenoceptors were 4200, 1300, and 40 nM, respectively. The affinity of mirabegron for β_3 -adrenoceptors was higher than those for the other subtypes.

(c) Affinity for various receptors, ion channels, and transporters as well as effects on

enzyme activity (Attached document 4.2.1.1-6 to 7)

Mirabegron 10 μM was used to investigate its affinities for various receptors (adenosine, adrenaline, angiotensin, bradykinin, cholecystokinin, corticotropin-releasing factor, dopamine, estrogen, endothelin, GABA, glutamic acid, glycine, histamine, leukotriene, melatonin, muscarine, neurokinin, nicotine, opioid, oxytocin, platelet-activating factor, serotonin, sigma, testosterone, vasopressin, vasoactive small intestinal peptide), ion channels (Ca^{2+} , K^{+} , Na^{+}), and transporters (dopamine, norepinephrine, serotonin) (56 molecular species in total) as well as its effects on enzyme activities (acetylcholinesterase, monoamine oxidase) (3 molecular species in total). As a result, taking each specific ligand binding and enzyme activity as 100%, mirabegron was found to competitively bind to rat α_{1A} -adrenoceptors, human muscarine M_2 receptor, rat sodium channel site 2, human dopamine transporter, and human norepinephrine transporter, inhibiting their specific ligand binding by $\geq 50\%$; their K_i values were 1.01, 2.10, 6.59, 1.45, and 11.0 μM , respectively. Mirabegron inhibition rates against the specific ligand binding to the investigated receptors, ion channels, and transporters other than the above as well as against the investigated enzyme activities were all found to be $< 50\%$ at 10 μM .

3.(i).A.(1).2) Bladder relaxant effect

(a) Effects on cAMP concentration in isolated rat bladder tissue (Attached document 4.2.1.1-8)

Mirabegron (0.1-10 μM), isoproterenol (0.001-0.1 μM) or vehicle was added to isolated rat bladder tissue, and the effects on cAMP concentration were investigated. As a result, compared with the vehicle, 1 and 10 μM of mirabegron as well as 0.1 μM of isoproterenol significantly increased the cAMP concentration in the isolated rat bladder tissue (mirabegron 1 μM , $P < 0.05$; mirabegron 10 μM and isoproterenol 0.1 μM , $P < 0.01$; Dunnett's multiple comparison test).

(b) Relaxant effect on isolated rat bladder (Attached document 4.2.1.1-9)

Effects of mirabegron (0.001-100 μM) and isoproterenol (0.001-100 μM) on carbachol (1 μM)-induced tonic contraction in the isolated rat bladder smooth muscle were investigated. As a result, mirabegron and isoproterenol relaxed the smooth muscle in a concentration-dependent manner, and their EC_{50} values were 5.1 and 1.4 μM , respectively, taking the relaxant effect of 100 μM of papaverine, a non-specific smooth muscle relaxant, as 100%. The maximum relaxant rates of mirabegron and isoproterenol with respect to the maximum relaxant effect of papaverine 100 μM were 94.0% for mirabegron 100 μM and 78.0% for isoproterenol 100 μM .

Similarly, the relaxant effects of mirabegron (0.001-100 μM) and isoproterenol (0.001-100 μM) on KCl (40 mM)-induced tonic contraction were investigated. As a result, mirabegron and isoproterenol relaxed the smooth muscle in a concentration-dependent manner, and with respect to papaverine 100 μM , their EC_{50} values were 11 and 0.092 μM , respectively, and their maximum relaxation rates were 69.1% for mirabegron 100 μM and 88.2% for isoproterenol 10 μM .

(c) Effect of β -adrenoceptor antagonists on mirabegron-induced relaxation in isolated rat bladder (Attached document 4.2.1.1-10)

Selective β_1 - and β_2 -adrenoceptor antagonists, CGP-20712A (100 nM) and ICI-118,551 (100 nM), respectively, were used to investigate their influences on relaxant effects of mirabegron (0.001-100 μM) and isoproterenol (0.001-100 μM) on isolated rat bladder smooth muscle. As a result, the concentration-relaxation response curve for mirabegron on carbachol (1 μM)-induced tonic contraction in isolated rat bladder was not affected by pretreatment with CGP-20712A or ICI-118,551. On the other hand, the concentration-relaxation response curve for isoproterenol was not affected by pretreatment with CGP-20712A, but shifted toward the right following pretreatment with ICI-118,551.

(d) Relaxant effect in isolated human bladder (Attached document 4.3-18 [Reference], *J Pharmacol Exp Ther.* 2007;321:642-7)

Effects of mirabegron (0.001-100 μ M) and isoproterenol (0.001-100 μ M) on carbachol (0.1 μ M)-induced tonic contraction in isolated human bladder smooth muscle were investigated. As a result, mirabegron and isoproterenol relaxed the smooth muscle in a concentration-dependent manner. When the relaxant effect of papaverine 100 μ M was taken as 100%, the EC₅₀ values of mirabegron and isoproterenol were 0.78 and 0.28 μ M, respectively, and the maximum relaxation rates were 89.4% for mirabegron 100 μ M and 85.6% for isoproterenol 100 μ M.

3.(i).A.(1).3) Effect on intravesical pressure

(a) Effect on resting intravesical pressure in rats (Attached document 4.2.1.1-11)

Physiological saline was injected into the bladder of pentobarbital-anesthetized rats, and after the intravesical pressure was stabilized, vehicle, mirabegron (0.003-3 mg/kg), or tolterodine (0.0003-0.3 mg/kg) or oxybutynin (0.001-1 mg/kg), both of which are muscarine receptor antagonists, was administered intravenously to investigate the effects on resting intravesical pressure. As a result, mirabegron significantly decreased the resting intravesical pressure at the doses of ≥ 0.03 mg/kg compared with the vehicle ($P < 0.01$, Student's *t*-test), while neither tolterodine nor oxybutynin showed a significant decrease in the intravesical pressure compared with the vehicle.

(b) Effect on dog intravesical pressure (Attached document 4.2.1.1-12)

Carbachol (1.8 μ g/kg) was administered intravenously to pentobarbital-anesthetized dogs to induce elevation of the intravesical pressure. Then, mirabegron (0.0003-0.01 mg/kg) was administered intravenously to the animals to investigate its effect on the induced intravesical pressure elevation. As a result, mirabegron significantly suppressed the carbachol-induced elevation of the intravesical pressure, compared with the baseline, in a dose-dependent manner ($P < 0.05$, Dunnett's multiple comparison test).

3.(i).A.(1).4) Effect on bladder function

(a) Effect on rhythmic bladder contraction

i) Effect following intravenous administration (Attached document 4.2.1.1-13)

Physiological saline was injected into the bladder of urethane-anesthetized rats to induce rhythmic bladder contraction. Mirabegron (0.03-3 mg/kg), oxybutynin (0.027-2.7 mg/kg) or vehicle was administered intravenously to the animals to investigate the effects on the frequency and maximum amplitude of rhythmic bladder contractions. As a result, mirabegron significantly decreased the frequency of bladder contractions at 3 mg/kg ($P < 0.05$, Student's *t* test), but mirabegron had no significant effect on the maximum amplitude of bladder contraction, compared with the vehicle. On the other hand, oxybutynin significantly increased the frequency of bladder contractions and decreased the maximum amplitude of bladder contractions at ≥ 0.27 mg/kg, compared with the vehicle.

ii) Effect following intraduodenal administration (Attached document 4.2.1.1-14)

Physiological saline was injected into the bladder of urethane-anesthetized rats to induce rhythmic bladder contraction. Mirabegron (1-10 mg/kg) or vehicle was administered intraduodenally to the animals to investigate the effects on the frequency and maximum amplitude of rhythmic bladder contractions. As a result, mirabegron significantly decreased the frequency of bladder contractions at ≥ 3 mg/kg (3 mg/kg, $P < 0.05$; 10 mg/kg, $P < 0.01$; Dunnett's multiple comparison test), but mirabegron had no significant effect on the maximum amplitude of bladder contractions, compared with the vehicle.

iii) Effect on rhythmic bladder contraction following repeated administration (Attached document 4.2.1.1-15)

The effect of mirabegron on rhythmic bladder contractions after repeated or single dosing was investigated. Mirabegron (30 mg/kg) was administered orally once daily to the repeated dose group for 14 days, while vehicle was administered orally to the single dose group and vehicle group once daily for 14 days. On Day 15, physiological saline was injected into the bladder under

urethane anesthesia to induce rhythmic bladder contraction. Then, a single dose of mirabegron (30 mg/kg) was administered intraduodenally to the repeated dose group and single dose group, and a single dose of the vehicle was administered intraduodenally to the vehicle group, to measure the frequency of rhythmic bladder contractions and the maximum intravesical pressure during bladder contraction. As a result, in both single dose and repeated dose groups, mirabegron significantly decreased the bladder contraction frequency ($P < 0.05$, Student's t -test), and the extent of the decrease was comparable between the single dose group and repeated dose group. In both single dose group and repeated dose group, mirabegron had no significant effect on the maximum intravesical pressure during bladder contraction, compared with the vehicle.

(b) Effect on mean volume voided per micturition and number of micturitions in unanesthetized cynomolgus monkeys (Attached document 4.2.1.1-16)

Mirabegron (0.3-3 mg/kg) or vehicle was administered orally to unanesthetized cynomolgus monkeys, and then distilled water was administered at 50 mL/kg by gavage to investigate the mean volume voided per micturition and number of micturitions. As a result, mirabegron significantly decreased the number of micturitions at the doses of ≥ 1 mg/kg (1 mg/kg, $P < 0.05$; 3 mg/kg, $P < 0.01$; Dunnett's multiple comparison test), and increased the mean volume voided per micturition at the dose of 3 mg/kg ($P < 0.05$, Dunnett's multiple comparison test), compared with the vehicle.

(c) Effect on mean volume voided per micturition in overactive bladder model animal (Attached document 4.2.1.1-17)

Rats with cerebral infarction were served as an animal model of overactive bladder. Mirabegron (0.3-3 mg/kg), oxybutynin (10 mg/kg) or vehicle was administered orally to the animals, and then distilled water was administered at 30 mL/kg by gavage to investigate the mean volume voided per micturition. As a result, mirabegron (3 mg/kg) and oxybutynin (10 mg/kg) significantly increased the mean volume voided per micturition ($P < 0.05$: mirabegron, Dunnett's multiple comparison test; oxybutynin, Student's t -test), compared with the vehicle.

(d) Effect on voiding function in rats with partial urethral obstruction (Attached document 4.2.1.1-18)

Mirabegron (0.1-3 mg/kg), tolterodine (0.01-0.3 mg/kg), oxybutynin (0.03-1 mg/kg), or vehicle was administered intravenously to unanesthetized rats with partial urethral obstruction and effects on the frequency of non-voiding contractions, volume voided per micturition, voiding pressure, and residual urine volume were investigated. As a result, mirabegron significantly decreased the frequency of non-voiding contractions at ≥ 1 mg/kg ($P < 0.01$, Student's t -test), but mirabegron had no significant effect on the volume voided per micturition, voiding pressure, and residual urine volume, compared with the vehicle. On the other hand, tolterodine significantly increased the volume voided per micturition at 0.3 mg/kg ($P < 0.05$, Student's t -test), but tolterodine had no significant effect on the frequency of non-voiding contractions, voiding pressure, and residual urine volume, compared with the vehicle. Oxybutynin significantly increased the residual urine volume at ≥ 0.3 mg/kg ($P < 0.05$, Student's t -test), but oxybutynin had no significant effect on the frequency of non-voiding contractions, volume voided per micturition, and voiding pressure.

3.(i).A.(1).4) Pharmacological actions of human plasma metabolites

(a) Agonistic effect on human β -adrenoceptors (Attached document 4.2.1.1-1)

Eight metabolites of mirabegron, M5, M8, M11, M12, M13, M14, M15, and M16 were identified in human plasma. Their agonistic effects on each subtype of human β -adrenoceptors (β_1 , β_2 , β_3) were investigated at the metabolite concentrations of 0.01 to 10,000 nM. In the cells expressing human β_3 -adrenoceptors, M13 increased the intracellular cAMP concentration in a concentration-dependent manner, and the intrinsic activity was 0.8, comparable to that of mirabegron, but the EC_{50} value was 1100 nM, which was higher than that of mirabegron (1.5 nM). The intrinsic activities of the other metabolites for human β_3 -adrenoceptors were all ≤ 0.5 , while those of each

metabolite for human β_1 - and β_2 -adrenoceptors were ≤ 0.1 and ≤ 0.2 , respectively; EC_{50} was not achieved in the concentration range tested (0.01-10,000 nM).

(b) Affinity to various receptors, ion channels, and transporters as well as effect on enzyme activity (Attached document 4.2.1.1-19 to 26)

Eight mirabegron metabolites in human plasma (M5, M8, M11, M12, M13, M14, M15, M16) were used to investigate affinities to various receptors (adenosine, adrenaline, angiotensin, bradykinin, cholecystokinin, corticotropin-releasing factor, dopamine, estrogen, endothelin, GABA, glutamic acid, glycine, histamine, leukotriene, melatonin, muscarine, neurokinin, nicotine, opioid, oxytocin, platelet-activating factor, serotonin, sigma, testosterone, vasopressin, vasoactive intestinal peptide), ion channels (Ca^{2+} , K^+ , Na^+), and transporters (dopamine, norepinephrine, serotonin) (total 56 molecular species) as well as effects on enzyme activities (acetylcholinesterase, monoamine oxidase) (total 3 molecular species). As a result, taking the each specific ligand binding and enzyme activity as 100%, M5 at 10 μM competitively inhibited the specific ligand binding to the dopamine transporter by 83%, and M16 at 10 μM competitively inhibited the specific ligand binding to the dopamine transporter and norepinephrine transporter by 73% and 68%, respectively. Inhibition rates of the other metabolites at 10 μM against the specific ligand binding to the investigated receptors, ion channels, and transporters other than the above as well as those against the investigated enzyme activities were found to be $< 50\%$.

3.(i).A.(2) Secondary pharmacodynamics

No relevant data have been submitted in this application.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1 Effect on the central nervous system (Attached document 4.2.1.3-1)

Mirabegron (30-300 mg/kg) was administered orally to rats to investigate the effect on the central nervous system. As a result, findings included a decrease in locomotor activity at ≥ 30 mg/kg, a decrease in grip strength, recumbency, palpebral closure, and deep respiration at ≥ 100 mg/kg, and hypotonia (general and abdominal), prone position, and loss of righting reflex at 300 mg/kg.

3.(i).A.(3).2 Effect on cardiovascular system and respiratory system

(a) Effect on hERG channel (Attached document 4.2.1.3-2)

HEK293 cells expressing human ether-a-go-go related gene (hERG) channel were treated with mirabegron (0.03-30 μM) to investigate the effect on hERG current. As a result, mirabegron did not inhibit the hERG current.

(b) Effect on hERG channel (additional study) (Attached document 4.2.1.3-23)

Since a thorough QT/QTc study in human (Study CL-037) suggested the effect of mirabegron on QTc interval, an additional study was conducted to re-investigate the effect of mirabegron (0.03-30 μM) on hERG current. To clarify the time when the drug solution in the chamber was changed, the drug perfusion time was changed from 10 minutes to 11 minutes. As a result of the additional study, mirabegron 30 μM inhibited the hERG current by 14.7%, compared with the baseline.

(c) Effects of human plasma metabolites on hERG channel (Attached document 4.2.1.3-3 to 5)

HEK293 cells expressing hERG channel were treated with mirabegron metabolites in human plasma, M5, M11, M12, M14, and M16, (0.3-30 μM) to investigate the effects on hERG current. As a result, compared with the baseline, M5 and M16 inhibited the hERG current in a concentration-dependent manner, and the 50% inhibition concentration (IC_{50}) was 21 and 31 μM , respectively. M14 at 30 μM inhibited the hERG current by 17.3%, and M11 and M12 did not inhibit the hERG current.

(d) Effect on cardiac action potential (Attached document 4.2.1.3-6)

Mirabegron (0.3-30 μ M) was added to isolated guinea pig papillary muscle to investigate the effects on the resting membrane potential, action potential amplitude, maximum upstroke velocity of the action potential as well as action potential durations at 30%, 50%, and 90% repolarization (APD₃₀, APD₅₀, APD₉₀). As a result, mirabegron did not affect the resting membrane potential or action potential in the isolated guinea pig papillary muscle.

**(e) Effects of human plasma metabolites on cardiac action potential
(Attached document 4.2.1.3-7 to 9)**

Mirabegron metabolites in human plasma, M5, M11, M12, M14, and M16, (0.3-30 μ M) or vehicle was added to isolated guinea pig papillary muscle to investigate the effects on the resting membrane potential, action potential amplitude, maximum upstroke velocity of the action potential as well as action potential durations (APD₃₀, APD₉₀). As a result, compared with the vehicle, M5 at 3 μ M prolonged the APD₃₀ by 6.1%, shortened the difference between APD₃₀ and APD₉₀ (APD₃₀₋₉₀) by 7.9%, increased the action potential amplitude by 1.7%; and M5 at 30 μ M prolonged the APD₃₀ by 5.6%, and the APD₉₀ by 4.7%. In addition, M16 at 30 μ M prolonged the APD₉₀ by 5.0%. M5 and M16 did not affect the other parameters. M11, M12, and M14 did not affect the resting membrane potential or action potential in the isolated guinea pig papillary muscle.

(f) Effects on cardiovascular system and respiratory system of unanesthetized cynomolgus monkeys (Attached document 4.2.1.3-10)

Mirabegron (3-100 mg/kg) or vehicle was administered orally in a single dose to unanesthetized cynomolgus monkeys to investigate the effects on the cardiovascular system and respiratory system. As a result, compared with the vehicle, an increase in heart rate at mirabegron \geq 10 mg/kg and vomiting, recumbency, and prolongation of PR and QRS intervals at mirabegron 10 mg/kg were observed, but at any dose, the body temperature, blood pressure, blood gas, and blood electrolyte concentrations were not affected.

(g) Effect on myocardial ion channel (Attached document 4.2.1.3-11 [Reference data])

The effects of mirabegron and its metabolites in human plasma, M5, M11, M12, M14, and M16 (10 μ M) on ion current in sodium channel (hNav1.5), calcium channel (hCav1.2), and potassium channels (hKvLQT1/hminK, hKv4.3/KChIP2.2) were investigated. As a result, compared with the baseline, mirabegron inhibited the sodium current (I_{Na}) by 48.5% and the calcium current (I_{Ca}) by 15.3%. In addition, M16 inhibited the sodium current by 10.5% and the calcium current by 8.8%. Mirabegron and M16 did not affect the 2 potassium currents (I_{Ks}, I_{to}), and M5, M11, M12, and M14 did not affect any ion current.

**(h) Effect on arterially perfused canine left ventricular wedge preparations
(Attached document 4.2.1.3-12 to 13 [Reference data])**

Mirabegron (3-300 ng/mL), its metabolites in human plasma, M5, M11, M12, M14, and M16, (3-100 ng/mL) as well as isoproterenol (0.248-248 ng/mL) were added to arterially perfused canine left ventricular wedge preparations to investigate the effects on QT interval in the transmural bipolar lead electrocardiograms (ECGs), interval from the peak to the end of the electrocardiographic T wave (Tp-e interval), which is deemed as an indicator of transmural dispersion of repolarization, and APD₉₀ as well as arrhythmogenic effects. To assess a risk of Torsade de pointes (TdP), TdP score was calculated based on the QT interval, Tp-e interval, and early afterdepolarization. As a result, mirabegron slightly reduced the QT interval and APD₉₀ at 300 ng/mL, but did not affect the Tp-e interval or TdP score at any concentration, indicating no arrhythmogenic effect. M5 slightly reduced the QT interval, Tp-e interval, and APD₉₀ at 100 ng/mL, but did not affect the TdP score, indicating no arrhythmogenic effect. In addition, M11, M12, M14, and M16 did not affect the ECGs. On the other hand, isoproterenol reduced the QT interval and APD₉₀ and increased the TdP score at \geq 2.48 ng/mL, and led to ventricular extrasystoles and ventricular tachycardia at \geq 24.8 ng/mL.

3.(i).A.(4) Supplemental safety pharmacology

3.(i).A.(4).1 Effect on the central nervous system

(Attached document 4.2.1.3-15 [Reference data])

Mirabegron (1-100 mg/kg) was administered orally in a single dose to mice, and the findings included prone position and an increase in rectal temperature at ≥ 10 mg/kg, increase in locomotor activity at 30 mg/kg, decreases in locomotor activity, alertness, limb muscle tone, abdominal muscle tone, bar-hanging strength, and body temperature (mild) as well as pale skin and piloerection at 100 mg/kg.

Following a single oral administration of mirabegron (10-100 mg/kg) to rats, mirabegron did not affect the pain threshold in the pressure stimulation procedure.

3.(i).A.(4).2 Effect on cardiovascular system and respiratory system

(a) Effects of mirabegron on cardiovascular system and respiratory system

i) Unanesthetized cynomolgus monkeys (oral administration)

(Attached document 4.2.1.3-16 [Reference data])

Mirabegron (3-100 mg/kg) was administered orally in a single dose to unanesthetized cynomolgus monkeys, and the findings included an increase in heart rate at ≥ 30 mg/kg and prolonged QRS interval and vomiting at 100 mg/kg.

ii) Unanesthetized dogs (oral administration)

(Attached document 4.2.1.3-15 [Reference data])

Mirabegron (0.01-10 mg/kg) was administered orally in a single dose to unanesthetized dogs. The findings included an increase in heart rate and reduced PR interval at ≥ 0.03 mg/kg as well as an increase in respiratory rate and decreases in systolic blood pressure and mean blood pressure at ≥ 0.3 mg/kg. Although shortened QT interval was observed at 10 mg/kg, the QTc interval was not affected. Blood carbon dioxide partial pressure decreased at 10 mg/kg, but the blood oxygen partial pressure and blood pH were not affected.

iii) Unanesthetized dogs (intravenous administration)

(Attached document 4.2.1.3-17 [Reference data])

Following a single intravenous dose of 10 mg/kg of mirabegron to unanesthetized dogs, an increase in heart rate, loss of P wave, prolonged QRS interval, and ventricular tachycardia were observed. Of 4 animals tested, 2 died of ventricular fibrillation. Mirabegron decreased the mean blood pressure in the surviving 2 animals and additionally prolonged the QTc interval in 1 of the animals.

iv) Effect on monophasic action potential duration in anesthetized dogs (intravenous administration) (Attached document 4.2.1.3-18 [Reference data])

Following cumulative intravenous doses of mirabegron (0.03-3 mg/kg) to anesthetized dogs, decreases in 90% monophasic action potential duration (MAPD₉₀) of the ventricular myocardium and QT interval as well as hyperacute T waves were observed at 3 mg/kg under the normal sinus rhythm condition. During pacing with an interval of 300 ms, a decrease in MAPD₉₀ was observed at mirabegron ≥ 0.3 mg/kg. In addition, during pacing with an interval of 400 ms, MAPD₉₀ was not measured in 2 of 4 animals tested, and in the remaining 2 animals, mirabegron 3 mg/kg decreased MAPD₉₀.

Following intravenous doses of mirabegron (10, 30 mg/kg) to anesthetized dogs, hyperacute T waves and ventricular tachycardia were observed in 1 animal each, and consequently both affected animals died.

v) Effect on cardiovascular system in anesthetized rabbits

(Attached document 4.2.1.3-14 [Reference data])

Following a single intravenous administration of mirabegron (0.1-1 mg/kg) to anesthetized rabbits, increases in heart rate and double product (heart rate \times systolic blood pressure), which serve as an index of myocardial oxygen consumption, were observed at 1 mg/kg, but the blood pressure was not affected at any concentration.

(b) Study on mechanism of actions of mirabegron on cardiovascular system

i) Effect of nonselective β -adrenoceptor antagonists in dogs

(Attached document 4.2.1.3-19 [Reference data])

Following a single oral administration of mirabegron (30-100 mg/kg) to unanesthetized dogs, increases in respiratory rate and heart rate, a decrease in mean blood pressure, shortened PR interval, shortened QT interval, and vomiting were observed at ≥ 30 mg/kg. When propranolol (1 mg/kg), a nonselective β -adrenoceptor antagonist, was intravenously administered immediately after oral administration of mirabegron 100 mg/kg, increases in respiratory rate and heart rate as well as a decrease in blood pressure were slight compared with the changes observed following the administration of mirabegron 100 mg/kg alone.

Following a single intravenous administration of mirabegron (10 mg/kg) to unanesthetized dogs, increases in respiratory rate and heart rate, a decrease in mean blood pressure, and ventricular tachycardia were observed. After development of ventricular tachycardia, propranolol 1 mg/kg was administered intravenously. However, 1 of 3 animals tested further experienced ventricular fibrillation and died. In the remaining 2 animals, cardiac arrhythmias such as extrasystoles and atrioventricular block were observed but resolved later.

Propranolol (1 mg/kg) was administered intravenously to unanesthetized dogs, and 5 minutes later, mirabegron (10 mg/kg) was administered intravenously. As a result, increases in respiratory rate and heart rate and a decrease in mean blood pressure as well as cardiac arrhythmias such as extrasystoles and atrioventricular block were observed, but ventricular tachycardia was only observed in 1 of 3 animals tested, which all resolved later.

ii) Effects of ganglionic antagonists and selective β_1 -adrenoceptor antagonists in dogs

(Attached document 4.2.1.3-20)

Following intravenous administration of mirabegron (0.0001-1 mg/kg) to anesthetized dogs, decreases in diastolic blood pressure, mean blood pressure, and left ventricular pressure as well as increases in heart rate and maximum pressure rising rate of left ventricular pressure (+dp/dt [max]) were observed at ≥ 0.001 mg/kg. On the other hand, mirabegron (0.01-1 mg/kg) was administered intravenously to animals pretreated with intravenous administration of hexamethonium (10 mg/kg), a ganglionic antagonist, and of vagal depressive atropine (1 mg/kg). As a result, a decrease in blood pressure was observed at ≥ 0.01 mg/kg of mirabegron, but increases in heart rate and +dp/dt (max) were observed only at ≥ 0.1 mg/kg. In animals pretreated with intravenous administration of hexamethonium, atropine, and metoprolol, a selective β_1 -adrenoceptor antagonist, (5 mg/kg), the increases in heart rate and +dp/dt (max) attributable to mirabegron were reduced compared with those following pretreatment only with hexamethonium and atropine.

iii) Effects of ganglionic antagonist, catecholamine depletor, and selective β_1 - and β_2 -adrenoceptor antagonists in rats (Attached document 4.2.1.3-22)

Following intravenous administration of mirabegron (0.03-0.3 mg/kg) to anesthetized rats, an increase in heart rate was observed at ≥ 0.1 mg/kg. Such increase in heart rate was also observed following pretreatment with hexamethonium 10 mg/kg, atropine 1 mg/kg, and reserpine, catecholamine depletor, 5 mg/kg with and without ICI-118,551 (0.1 mg/kg), but the increase in heart rate was almost completely suppressed following the pretreatment with metoprolol 1 mg/kg.

3.(i).A.(4).3) Effect on urinary excretion

(Attached document 4.2.1.3-15 [Reference data])

Mirabegron (1-100 mg/kg) was administered orally in a single dose to rats loaded with physiological saline. The findings included decreases in urine volume and electrolyte (sodium, potassium, chlorine) excretion at 0 to 3 hours after the doses of ≥ 10 mg/kg as well as an increase in potassium excretion and a decrease in chlorine excretion at 3 to 6 hours after the doses of ≥ 30 mg/kg.

3.(i).A.(4).4) Effect on autonomic nervous system

(Attached document 4.2.1.3-15 [Reference data])

Mirabegron (0.01-10,000 nM) alone did not affect the isolated guinea pig ileum. On the other hand, mirabegron inhibited histamine-, barium chloride-, and serotonin-induced contraction at ≥ 10 nM and acetylcholine-induced contraction at ≥ 100 nM.

3.(i).A.(4).5) Effect on gastrointestinal system

(Attached document 4.2.1.3-15 [Reference data])

Following a single oral administration of mirabegron (10-100 mg/kg) to mice, the gastrointestinal propulsion was not affected.

3.(i).A.(5) Drug-drug pharmacodynamic interaction

No relevant data have been submitted in this application.

3.(i).B. Outline of the review by PMDA

3.(i).B.1) Primary pharmacodynamics

PMDA asked the applicant to explain the mechanism of action of mirabegron based on the distribution of the adrenoceptors and their roles in the bladder in OAB patients, because the study for agonistic effect of mirabegron on β -adrenoceptors of human and various animals (Attached document 4.2.1.1-1) showed that mirabegron had agonistic effects not only on β_3 -adrenoceptors but also β_1 - and β_2 -adrenoceptors.

The applicant responded as follows:

According to a report on gene expression, human bladder smooth muscle expresses β -adrenoceptors abundantly, most of which (97%) are β_3 -adrenoceptor subtype (*Urology*. 2002;59[Suppl 1]:25-9, *J Urol*. 2003;170:649-53). It is recognized that during the sympathetically-innervated urine storage phase, noradrenalin released from hypogastric nerve ending stimulates β -adrenoceptors present in the bladder smooth muscle, relaxing the bladder (*Exp Physiol*. 1999;84:195-213). The results of studies using selective agonists and antagonists for each of β -adrenoceptor subtypes (*J Pharmacol Exp Ther*. 1999;288:1367-73, *Br J Pharmacol*. 1999;126:819-25) suggest that the relaxant effect in human bladder is mediated mainly by the β_3 -adrenoceptors. So far, there are no reports of detailed studies on distribution and roles of β -adrenoceptors in the bladder isolated from OAB patients. However, a report of the study using bladder tissue specimens isolated from patients with bladder outlet obstruction and neurogenic bladder, which are considered to cause OAB, has shown that the gene expression pattern of the β_3 -adrenoceptors and roles in relaxant function are almost comparable to those in normal bladder tissue (*J Urol*. 2001;165:240-4). Based on the above, the human bladder smooth muscle relaxes mainly through the β_3 -adrenoceptors. Accordingly, mirabegron stimulates the β_3 -adrenoceptors present in the bladder smooth muscle in OAB patients, relaxing the bladder to improve the urine storage function.

In the study on the effects of intravenously administered mirabegron on rhythmic bladder contraction in rats (Attached document 4.2.1.1-13), oxybutynin increased the bladder contraction frequency, while mirabegron decreased such frequency. Concerning these study results, PMDA

asked the applicant to explain how mirabegron and the anticholinergic act on the frequency of rhythmic bladder contractions.

The applicant responded as follows:

In this study, mirabegron decreased the frequency of rhythmic bladder contractions mainly because the bladder relaxant effect of mirabegron led to a prolonged duration of the intravesical pressure below the voiding threshold. On the other hand, anticholinergics such as oxybutynin did not decrease the resting intravesical pressure sufficiently, and thus did not affect the resting intravesical pressure. When oxybutynin acts on the bladder, the intravesical pressure would be maintained without decreasing the frequency of rhythmic bladder contractions. The following 3 changes may have led to the finding that oxybutynin increased the frequency of rhythmic bladder contractions: (i) oxybutynin inhibited the acetylcholine release suppression in association with stimulation of muscarine M₂ receptor present in presynaptic terminal of the pelvic nerve, resulting in an increase in acetylcholine released from the pelvic nerve ending; (ii) intracerebrally distributed oxybutynin inhibited the micturition reflex suppression in association with stimulation of muscarine M₁ receptor present in the upper central nerve, resulting in enhanced micturition reflex, which led to the increased frequency of rhythmic bladder contractions; (iii) in association with decreased bladder contraction potential related to muscarine M₃ receptor blockade induced by oxybutynin, the duration of bladder contraction was shortened. In addition, atropine, which is an anticholinergic and has central nervous system penetration, has been reported to lead to a decrease in the rhythmic bladder contractility and an increase in contraction frequency as with oxybutynin (*Oyo Yakuri/Pharmacometrics*. 1986;37:17-26, *Br J Pharmacol*. 1990;101:49-54, *Pharmacol Res*. 1993;27:173-87, *BJU Int*. 2003;92:1031-6).

In the study on the effect of intravenously administered mirabegron on rhythmic bladder contraction in rats (Attached document 4.2.1.1-13), oxybutynin decreased the maximum intravesical pressure at the time of contraction, while mirabegron did not affect this parameter. The applicant explained that this finding suggested that mirabegron is unlikely to aggravate the voiding function in OAB patients. Concerning the applicant's explanation, PMDA asked the applicant to discuss whether or not clinical studies demonstrated that mirabegron is unlikely to aggravate the voiding function in OAB patients compared with anticholinergics.

The applicant responded as follows:

The exclusion criteria were set to include only patients at a low risk of urinary retention or dysuria in Japanese Study CL-048 and Foreign Study CL-046, which evaluated the efficacy and safety of mirabegron in OAB patients, thus, no particular differences were noted in the incidence of adverse events such as urinary retention and dysuria between mirabegron and tolterodine, an anticholinergic. Anticholinergics may aggravate dysuria or cause urinary retention in patients with bladder outlet obstruction because they attenuate detrusor contraction. However, in an urodynamic study in patients with lower urinary tract symptoms and bladder outlet obstruction (Study CL-060), mirabegron did not adversely affect the detrusor pressure at the maximum urinary flow rate or maximum urinary flow rate, and was tolerated. Therefore, the study suggests that mirabegron is unlikely to aggravate the voiding function in OAB patients.

PMDA considers as follows:

Primary pharmacodynamics data show that mirabegron has an agonistic effect and selectivity for β_3 -adrenoceptors and bladder relaxant effect, increases in the mean volume voided per micturition, and decreases micturition frequency. Based on the results, PMDA has concluded that the obtained study data suggests the efficacy of mirabegron mediated by β_3 adrenaline agonistic effect in the treatment of OAB patients. On the other hand, the applicant claims that data from the study on the effects of intravenously administered mirabegron on rhythmic bladder contraction in rats (Attached document 4.2.1.1-13) suggested that mirabegron is less likely to aggravate the voiding function in OAB patients compared with anticholinergics. However, the concerned study only

investigated the maximum intravesical pressure during rhythmic bladder contraction in rats. Thus, the study data do not evidently demonstrate clinical effects of mirabegron and anticholinergics on the voiding function in OAB patients. In addition, Study CL-060 included a limited number of subjects, and Studies CL-046 and CL-048, which used anticholinergics as a control drug, included only patients at a low risk of urinary retention or dysuria. The clinical study data do not clearly demonstrate that mirabegron is less likely to aggravate the voiding function and to cause urinary retention in OAB patients compared with anticholinergics either.

3.(i).B.2) Safety pharmacology

Concerning studies for effects on hERG channel in HEK293 cells, PMDA asked the applicant to explain the background to conduct 2 similar studies and to discuss why mirabegron at 30 μ M inhibited the current only in the second study.

The applicant responded as follows:

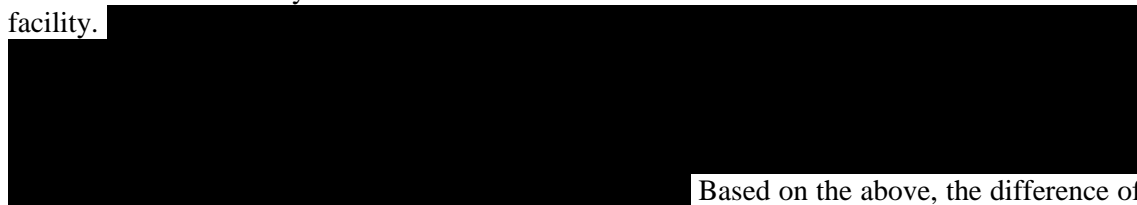
After the first study for hERG current inhibition was conducted in 2011, the thorough QT/QTc study (Study CL-037) in humans suggested the effect of mirabegron on QTc interval. In response to that study result, from 2011 to 2012, studies were further conducted to investigate the effects of mirabegron metabolites on hERG current and action potential duration and the effects of mirabegron and its metabolites on myocardial ion channels and arterially perfused canine left ventricular wedge preparations. However, neither study showed any effect suggesting that mirabegron may prolong QT/QTc interval in clinical use. Then, the second study for hERG current inhibition was conducted to re-investigate whether mirabegron would have a hERG current-inhibiting effect, which is considered to be a main cause for QT/QTc interval prolonged. Mirabegron at 30 μ M inhibited hERG current by 14.7% in the second study, although it did not affect the hERG current in the first study (the table below).

Table. Data from study for hERG current measurement

Test article	Corrected inhibition rate (%) [mean \pm standard deviation (SD), n = 5]					
	Vehicle (DMSO)	Mirabegron				Positive control (E-4031)
Treatment concentration	0.1%	0.03 μ M	0.3 μ M	3 μ M	30 μ M	0.1 μ M
First	0.0 \pm 1.1	-0.5 \pm 1.5	-2.4 \pm 3.2	0.0 \pm 1.2	-1.3 \pm 1.4	79.7 \pm 2.7*
Second	0.0 \pm 3.9	2.2 \pm 5.1	-0.8 \pm 3.6	7.2 \pm 6.5	14.7 \pm 2.8*	82.7 \pm 3.7*

* $P < 0.01$

Measurement conditions in both studies were almost the same except for the drug perfusion time, which was different by 1 minute, this difference in measurement conditions between the 2 studies is thus unlikely to cause different results. On the other hand, it is known that measurement results of hERG current can vary to some extent even under the same measurement condition in the same facility.



Based on the above, the difference of results between 2 studies for hERG current inhibition may be caused by the variations in inhibitory response. In addition, mirabegron 30 μ M is considered to be almost comparable to the threshold concentration of hERG current inhibition, which is positioned at the rising part of the dose-response curve where variations are likely to occur; mirabegron at the concerned concentration can produce varied responses, influencing the results of the 2 studies. The maximum concentration investigated in both studies, 30 μ M, is approximately 657 times higher than the maximum plasma concentration of unbound mirabegron at the recommended clinical

dose of 50 mg, the mild hERG current inhibition observed in the second study is unlikely to result in prolongation of QT/QTc interval in clinical use.

PMDA considers as follows:

Although the applicant claims that the difference of results between 2 studies for the effect of mirabegron on hERG current (Attached document 4.2.1.3-2, 4.2.1.3-23) may be caused by the variations, there is no evidence supporting the applicant's explanation that mirabegron 30 μ M can be almost comparable to the threshold concentration, at which hERG current is inhibited, and the results of the above 2 studies failed to demonstrate that mirabegron does not affect hERG current. In addition, pharmacology data suggest a risk for mirabegron to affect the cardiovascular system in consideration of mirabegron metabolites in plasma, M5, M14, and M16, inhibited hERG current, and considering that mirabegron has agonistic effects not only on β_3 -adrenoceptors but also on human β_1 - and β_2 -adrenoceptors and has an affinity to muscarine M₂ receptor and that toxicity data (Attached document 4.2.3.5.2-6) suggested that mirabegron may have a risk attributable to its agonistic effect for β_1 -adrenoceptors [see "3.(iii).B.(2) Effects on reproductive organs"]. PMDA will continue to discuss a risk for mirabegron to affect QTc interval and necessary measures for ensuring the safety in the section for clinical data, in consideration of the expected drug exposure in the patients [see "4.(iii).B.(2).2) Risk on cardiovascular system"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A. Summary of the submitted data

Following administration of ¹⁴C-labeled mirabegron, the radioactivity levels in biological samples were determined by liquid scintillation counter. Plasma mirabegron concentrations in mice, rats, rabbits, dogs, and cynomolgus monkeys were measured by validated high performance liquid chromatography with ultraviolet detection (HPLC-UV) or liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limits of quantitation of HPLC-UV and LC-MS/MS differed depending on the study, ranging from 1 to 10 ng/mL and from 0.1 to 4 ng/mL, respectively. Since mirabegron is hydrolyzed in mouse and cynomolgus monkey plasma by esterase, dichlorvos, an esterase inhibitor, was added to blood samples immediately after blood collection. Plasma concentrations of mirabegron metabolites in mice, rats, rabbits, and cynomolgus monkeys were measured by LC-MS/MS.

Unless otherwise specified, pharmacokinetic parameters are expressed as mean \pm SD.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1 Single dose administration

(Attached document 4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-4 to 4.2.2.2-6)

Mirabegron (3, 10, 30 mg/kg) was administered orally in a single dose to fasted male rats, the time to reach maximum plasma concentration (t_{max}) of mirabegron was 2.0, 4.0, and 0.1 hours, respectively (calculated from the mean concentration at each time point), the maximum plasma concentration (C_{max}) was 37.0, 291.2, and 1348.7 ng/mL, respectively, the area under the plasma concentration-time curve from time 0 to infinite (AUC_{inf}) was 242.8, 1700.7, and 7976.9 ng·h/mL, respectively, the elimination half-life ($t_{1/2}$) was 3.8, 5.0, and 3.6 hours, respectively, and the absolute bioavailability (BA) was 23.0%, 48.4%, and 75.7%, respectively ($n = 3$ /time point). Mirabegron (1 mg/kg) was administered intravenously in a single dose to male rats. As a result, the total body clearance (CL_{tot}) was 47.4 mL/min/kg and distribution volume at steady state (V_{ss}) was 10.3 L/kg ($n = 3$ /time point). ¹⁴C-labeled mirabegron (10 mg/kg) was administered orally to male rats under fasted conditions. As a result, the total radioactivity levels in both blood and plasma reached the peak at 3 hours post-dose and then biphasically decreased with the elimination half-life in the distribution phase ($t_{1/2\alpha}$) of 2.67 and 2.60 hours, respectively, as well as that in the elimination phase ($t_{1/2\beta}$) of 70.02 and 39.45 hours, respectively. The ratio of AUC_{inf} of plasma mirabegron to that of plasma radioactivity was approximately 18% ($n = 3$ /time point).

Mirabegron (0.25, 0.5, 1 mg/kg) was administered orally in a single dose to male dogs (n = 4). As a result, t_{\max} was 0.50 ± 0.35 , 4.00 ± 0.00 , and 0.33 ± 0.14 hours (mean \pm SD), respectively, C_{\max} was 9.1 ± 1.7 , 12.3 ± 2.5 , and 40.5 ± 3.8 ng/mL, respectively, AUC_{inf} was 46.7 ± 3.0 , 145.3 ± 33.3 , and 366.2 ± 90.8 ng·h/mL, respectively, $t_{1/2}$ was 4.4 ± 0.1 , 9.5 ± 2.4 , and 9.4 ± 2.0 hours, respectively, and absolute BA was $41.8\% \pm 6.3\%$, $64.6\% \pm 15.1\%$, and $77.1\% \pm 20.9\%$, respectively. Mirabegron (0.1 mg/kg) was administered intravenously in a single dose to male dogs (n = 4). As a result, CL_{tot} was 37.2 ± 4.6 mL/min/kg and V_{ss} was 14.3 ± 4.3 L/kg.

^{14}C -labeled mirabegron (10 mg/kg) was administered orally in a single dose to male cynomolgus monkeys (n = 3) under fasted conditions. As a result, t_{\max} of the total radioactivity in blood and plasma were both 0.67 ± 0.29 hours, and $t_{1/2}$ of the total radioactivity in blood and plasma were 20.7 ± 7.2 and 23.7 ± 11.5 hours, respectively. The ratio of AUC_{inf} of plasma mirabegron to that of plasma radioactivity was approximately 5%.

Mirabegron (0.5 mg/kg) was administered orally in a single dose to male dogs (n = 6) under both fasted and fed conditions. As a result, the mean t_{\max} was 1.6 hours in both conditions, but C_{\max} and AUC_{inf} in the fed condition decreased to 78.5% and 65.8% of those in the fasted condition, respectively.

To overnight fasted male rats, ^{14}C -labeled mirabegron was administered into 5 gastrointestinal tract loops (stomach, duodenum, jejunum, ileum, colon). The mean absorption rate at 1 hour (% of the dose) was 65.9% in the ileum, 61.7% in the jejunum, 55.5% in duodenum, 15.1% in the colon, and 7.1% in the stomach (n = 3/organ).

3.(ii).A.(1).2) Repeated administrations

(Attached document 4.2.2.2-3, 4.2.2.2-7, 4.2.2.4-11 to 4.2.2.4-17)

Mirabegron (0.5 mg/kg) was administered orally once daily to male dogs (n = 6) for 15 days. On Day 1, Day 8, and Day 15 of dosing, t_{\max} was 3.5 ± 2.4 , 2.1 ± 1.6 , and 1.5 ± 1.4 hours, respectively, C_{\max} was 25.0 ± 16.7 , 25.1 ± 6.8 , and 39.4 ± 23.2 ng/mL, respectively, and $t_{1/2}$ was 9.2 ± 2.8 , 8.8 ± 1.8 , and 12.4 ± 2.9 hours, respectively. On Day 1, AUC_{inf} was 175.3 ± 53.8 , and on Day 8 and Day 15, the area under the plasma concentration-time curve from time 0 to time 24 hours ($AUC_{24\text{h}}$) was 155.5 ± 24.8 and 173.6 ± 38.0 ng·h/mL, respectively. Mirabegron was administered orally once daily for 15 days in fed condition to male and female mice (n = 3/sex/time point) at the doses of 25, 50, and 100 mg/kg, to male and female rats (n = 3/sex/time point) at the doses of 10, 30, and 100 mg/kg, to female rabbits (n = 3) at the doses of 3, 10, and 30 mg/kg, and to male and female cynomolgus monkeys (n = 3/sex) at the doses of 3, 10, and 30 mg/kg. In mice, rats, and rabbits at the high doses (100, 100, and 30 mg/kg/day, respectively), C_{\max} and $AUC_{24\text{h}}$ of mirabegron on Day 8 and Day 15 were up to approximately 2 times the C_{\max} and $AUC_{24\text{h}}$ on Day 1. However, in the other animals and in the other dose groups, $AUC_{24\text{h}}$ following repeated administrations was almost comparable to that on Day 1.

^{14}C -labeled mirabegron was administered orally once daily at the dose of 10 mg/kg for 21 days to fed male rats (n = 3), and the plasma radioactivity at 24 hours after each administration gradually increased, but almost reached a plateau on Day 17.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Single dose administration (Attached document 4.2.2.2-5 to 6, 4.2.2.3-3 to 5)

^{14}C -labeled mirabegron (10 mg/kg) was administered orally in a single dose to white male rats. As a result, the tissue radioactivity levels reached the peak in the stomach at 0.5 hours post-dose, the lung at 1 hour post-dose, and the other tissues at 4 hours post-dose (n = 3/time point). The radioactivity per 1 g of tissue at 4 hours post-dose was found to be highest in the liver among all tissues except the gastrointestinal tract, which was 17.48 times higher than the radioactivity per 1

mL of plasma. The next highest radioactivity were found in the kidney, pituitary gland, pancreas, adrenal gland, and lung, which were 4.83 to 6.85 times higher than the radioactivity level in the plasma, and the lowest levels were found in the cerebrum and cerebellum. The radioactivity elimination in the tissue was slower than that in the plasma, but the radioactivity at 168 hours post-dose was <10% of the maximum level in all tissues except the testis (41% of the maximum in the testis). ¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to white male rats to investigate the tissue radioactivity distribution by whole body autoradiography. At 4 hours post-dose, the radioactivity was distributed throughout the body except for the brain, eyeballs, and spinal cord, and especially, highly distributed in the liver, brown fat, and kidney (n = 1/time point). At 168 hours post-dose, the tissue radioactivity decreased throughout the body, but were still found to be high in the liver, kidney, brown fat, and testis. Results of the whole body autoradiography agreed well with the tissue radioactivity data, but in the brown fat and Harderian gland where the tissue radioactivity were not measured, drug-derived compounds were found at high levels.

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to pigmented male rats. As a result, tissue radioactivity levels reached the peak in the stomach and small intestine at 1 hour post-dose, in the eyeballs at 24 hours post-dose, and in the other tissues at 4 hours post-dose (n = 3/time point). The radioactivity per 1 g of tissue at 4 hours post-dose was found to be highest in the liver and pituitary gland among all tissues except the gastrointestinal tract, which was 11.56 times and 9.03 times higher than the radioactivity per 1 mL of plasma. The next highest radioactivity levels were found in the pancreas, adrenal gland, lung, kidney, and eyeballs, which were 3.66 to 6.16 times higher than the radioactivity levels in the plasma, and radioactivity levels in the cerebrum and cerebellum were found to be low. At 24 hours post-dose, the radioactivity in the eyeballs was 18 times the maximum level in white rats. ¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to pigmented male rats to investigate the changes in radioactivity in the eyeballs over time for up to 180 days post-dose. As a result, the radioactivity levels in the eyeballs reached the peak (5358.53 ng eq./g) at 15 days post-dose, and t_{1/2} of the radioactivity in the eyeballs was calculated to be 157 days. At 360 hours post-dose, the radioactivity was <10% of the maximum level in all tissues except the testis and eyeballs, while the radioactivity levels in the testis and eyeballs were 23% and 68% of the maximum level, respectively. ¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to pigmented male rats. In microscopic autoradiography on the eyeballs at 24 hours post-dose, the radioactivity was especially distributed in the ciliary body, choroid, and conjunctiva, tissues containing melanin at high levels.

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to male cynomolgus monkeys (n = 3). As a result, at 168 hours post-dose, the highest tissue radioactivity level was found in the liver (1114.29 ng eq./g) followed by bile, eyeballs, pancreas, adrenal gland, and kidney in this order, while the radioactivity levels in the blood, plasma, fat, cerebrum, cerebellum, pituitary gland, and stomach content were below the detection limit (8.23-41.16 ng eq./g or mL). The radioactivity level in the eyeballs at 168 hours post-dose was 404.12 ng eq./g.

3.(ii).A.(2).2) Repeated-dose administrations (Attached document 4.2.2.2-7)

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally once daily to white male rats for 21 days. The radioactivity tissue distribution patterns at 4 and 24 hours post-dose on Day 7, Day 14, and Day 21 were similar to that obtained following a single dose administration; high radioactivity levels were found in the liver, kidney, adrenal gland, and pituitary gland (n = 3/time point). The tissue radioactivity at 24 hours post-dose increased in a dose-dependent manner in most of the tissues, but the ratio of the tissue radioactivity levels to the plasma radioactivity levels on Day 14 was almost comparable to that on Day 21. The tissue radioactivity levels after the last dose

reached the peak at 4 hours post-dose in all tissues except the testis (which reached the peak at 24 hours post-dose), and then decreased over time. At 360 hours after the last dose, relatively high radioactivity levels were found in the kidney, thyroid, liver, and adrenal gland at 42%, 42%, 11%, and 28% of those at 4 hours post-dose, respectively.

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally once daily to white male rats for 21 days. In the whole body autoradiography at 4 hours post-dose, high radioactivity levels were found in the pituitary gland, thyroid, brown fat, liver, kidney, and adrenal gland (n = 2/time point).

3.(ii).A.(2).3) Placental transfer (Attached document 4.2.2.3-6)

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to rats on Gestation day 14 (organogenesis period) (n = 3/time point), the radioactivity levels per 1 g of the placenta and fetus reached the peak at 4 hours post-dose, which were 1.5 and 0.2 times that per 1 mL of the dam plasma at 4 hour post-dose, respectively. At 24 hours post-dose, the radioactivity in the placenta, ovary, mammary gland, and fetus decreased to 28%, 27%, 26%, and 20% of their maximum levels, respectively.

Results of the whole body autoradiography following a single oral dose of 10 mg/kg of ¹⁴C-labeled mirabegron to rats on Gestation day 19 (perinatal period) (n = 1/time point) almost agreed with the tissue radioactivity data in rats on Gestation day 14.

3.(ii).A.(2).4) Plasma protein binding and distribution in blood cells (Attached document 4.2.2.2-5, 4.2.2.3-1, 4.2.2.3-2)

¹⁴C-labeled mirabegron was added to each plasma from mice, rats, rabbits, dogs, and cynomolgus monkeys. The plasma protein binding rates were almost consistent across the concentration range from 200 to 5000 ng/mL (final concentration) in all animal species tested and were 76.7% to 77.7% in mice, 78.5% to 79.5% in rats, 87.2% to 88.2% in rabbits, 61.1% to 62.0% in dogs, and 53.3% to 56.4% in cynomolgus monkeys.

In blood from rats, dogs, and cynomolgus monkeys, the ratios of the blood to plasma radioactivity levels of ¹⁴C-labeled mirabegron were almost consistent across the concentration range of 100 to 2500 ng/mL of mirabegron (final concentration) in all animal species tested, and were 1.22 to 1.34 in rats, 1.52 to 1.55 in dogs, and 1.43 to 1.48 in cynomolgus monkeys.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism (Attached document 4.2.2.4-1 to 3)

¹⁴C-labeled mirabegron was added to mouse, rat, dog, cynomolgus monkey, and human liver microsomes to obtain a final concentration of 10 µM and the mixture was incubated at 37°C for 60 minutes in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH). As a result, at least 3 metabolite peaks were observed in HPLC chromatograms from the microsomes of all the animal species tested. In the absence of NADPH, 1 metabolite peak was observed in the chromatogram only from the mouse liver microsome.

Mirabegron was added to mouse, rat, rabbit, dog, cynomolgus monkey, and human plasma to obtain a final concentration of 200 ng/mL, followed by incubation with and without dichlorvos, an esterase inhibitor. The metabolic rate of mirabegron without dichlorvos was found to be the highest in the human plasma among the above samples, followed by mouse and cynomolgus monkey plasma in this order. No decrease in unchanged mirabegron levels was observed in rat, rabbit, and dog plasma. On the other hand, with dichlorvos, mirabegron was not metabolized in plasma of any animal species.

3.(ii).A.(3).2) *In vivo* metabolism (Attached document 4.2.2.4-8 to 17)

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to male mice. As a

result, unchanged mirabegron accounted for 31.2% to 50.8% of the radioactivity in plasma at 2 to 4 hours post-dose, which were the highest abundance values. Of plasma metabolites, M16 (deacylated mirabegron) and M8 (the secondary amine of mirabegron has been cleaved to form carboxylate) were found at the highest levels, accounting for 5.9% to 10.4% and 5.8% to 9.7% of the radioactivity at 2 to 4 hours post-dose. Mirabegron (25, 50, 100 mg/kg) was administered once daily to male and female mice for 15 days. When compared based on AUC_{24h}, M11 (glucuronide conjugate of mirabegron) was found to show the largest AUC_{24h} among the metabolites, which accounted for approximately 11% to 25% of AUC_{24h} of mirabegron in males and for approximately 7% to 11% in females.

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to male rats. As a result, unchanged mirabegron accounted for 31.9% to 45.0% of the radioactivity in plasma at 1 to 6 hours post-dose (t_{max} of the plasma radioactivity was 3 hours). Of plasma metabolites, M6 (phenethylamine compound generated simultaneously with formation of phenylglyoxylic acid from mirabegron) was found at the highest level, accounting for 32.1% to 47.1% of the radioactivity at 1 to 6 hours post-dose. Until 24 hours after oral administration, 8.41% of the administered radioactivity was excreted in urine as unchanged mirabegron, accounting for approximately a half of the radioactivity excretion rate in urine. M8 and M6 were found at high levels compared with the other metabolites, but the excretion rate with respect to the administered radioactivity was 2.39% and 2.10%, respectively. The excretion rate of unchanged mirabegron into bile with respect to the dosed radioactivity was 6.11% until 6 hours post-dose and 0.95% between 6 and 24 hours post-dose. Mirabegron (10, 30, 100 mg/kg) was administered once daily to male and female rats for 15 days. When compared based on AUC_{24h}, M8 was found to have the largest AUC_{24h} among the metabolites, which accounted for approximately 10% to 26% of AUC_{24h} of mirabegron in males and for approximately 5% to 17% in females.

¹⁴C-labeled mirabegron (10 mg/kg) was administered orally in a single dose to male cynomolgus monkeys. As a result, unchanged mirabegron accounted for 3.2% to 4.1% of the radioactivity in plasma at 1 to 2 hours post-dose (t_{max} of the plasma radioactivity was 0.67 hours). Of plasma metabolites, M11 was found at the highest level, accounting for 78.5% to 82.1% of the radioactivity at 1 to 2 hours post-dose. Until 48 hours after oral administration, 4.60% of the administered radioactivity was excreted in urine as unchanged mirabegron, accounting for approximately 10% of the radioactivity excretion rate in urine. Of urine metabolites, M11 was found at the highest level with the excretion rate with respect to the administered radioactivity being 31.62%, accounting for approximately 70% of the radioactivity excretion rate in urine. Mirabegron (3, 10, 30 mg/kg) was administered orally once daily to male and female cynomolgus monkeys for 15 days. When plasma metabolite levels were compared based on AUC_{24h}, M11 was found to have the highest AUC_{24h}, which was approximately 20 to 30 times AUC_{24h} of unchanged mirabegron.

Mirabegron (3, 10, 30 mg/kg) was administered orally once daily to female rabbits for 15 days. As a result, when compared based on AUC_{24h}, M5 (metabolite in which the amide bond of mirabegron has been hydrolyzed, and the resultant amine has undergone acetyl conjugation) was found to have the largest AUC_{24h}, which was approximately 3 to 9 times AUC_{24h} of unchanged mirabegron. M16 was found to have the second largest AUC_{24h}, which was approximately 2 to 4 times that of unchanged mirabegron.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1 Urinary and fecal excretion (Attached document 4.2.2.2-5, 4.2.2.2-6)

A single dose of ¹⁴C-labeled mirabegron (10 mg/kg) was administered orally to male rats (n = 4). As a result, the cumulative excretion rate of radioactivity in urine and feces up to 168 hours post-dose was 18.8% and 75.3% of the dose, respectively. No radioactivity excretion into the expiration was observed.

A single dose of ^{14}C -labeled mirabegron (10 mg/kg) was administered orally to male cynomolgus monkeys ($n = 3$). As a result, the cumulative excretion rate of radioactivity in urine and feces up to 168 hours post-dose was 46.8% and 54.2% of the dose, respectively.

3.(ii).A.(4).2) Urinary and biliary excretion (Attached document 4.2.2.2-5)

A single dose of ^{14}C -labeled mirabegron (10 mg/kg) was administered orally to bile duct cannulated male rats ($n = 4$). As a result, the cumulative excretion rate of radioactivity in urine and bile up to 72 hours post-dose was 37.3% and 29.4% of the dose, respectively.

3.(ii).A.(4).3) Enterohepatic circulation (Attached document 4.2.2.2-5)

A single dose of ^{14}C -labeled mirabegron (10 mg/kg) was administered orally to bile duct cannulated male rats ($n = 4$) to collect the bile between 0 and 6 hours post-dose, from which 0.5 mL was then infused into the duodenum of other bile duct cannulated male rats ($n = 3$). The cumulative excretion rate of radioactivity in urine and bile up to 24 hours post-dose was 15.0% and 7.4% of the administered radioactivity, and that up to 72 hours was 18.4% and 8.1%, respectively.

3.(ii).A.(4).4) Excretion into milk (Attached document 4.2.2.5-1)

A single dose of ^{14}C -labeled mirabegron (10 mg/kg) was administered orally to lactating (the 14th day after parturition) rats ($n = 3$ /time point). The plasma radioactivity level in dams at 1 and 4 hours post-dose was 70.95 ± 30.38 (mean \pm SD) and 67.96 ± 27.30 ng eq./mL, respectively, and the radioactivity level in milk was 31.42 ± 10.60 and 115.27 ± 51.99 ng eq./mL, respectively. At 24 hours post-dose, both radioactivity levels in plasma and milk were below the detection limit (plasma, 13.5 ng eq./mL; milk, 20.6 ng eq./mL). The radioactivity level in the liver, kidney, and lung in suckling rats at 24 hours post-dose was 24.71 ± 0.71 , 7.54 (mean of the values from 2 animals), and 6.82 (mean of the values from 2 animals) ng eq./g, respectively.

3.(ii).B. Outline of the review by PMDA

3.(ii).B.(1) Pharmacokinetic nonlinearity of mirabegron

The applicant explained the reason for more than dose-proportional increases in AUC following a single oral dose of mirabegron in rats and dogs, as follows:

The nonlinear increase in AUC was considered attributable to the saturation of intestinal or hepatic first-pass metabolism or efflux. However, in the pharmacokinetic study in rats where the metabolites were measured, plasma concentrations of not only all measured metabolites but also unchanged mirabegron were nonlinearly increased with increasing doses (Attached document 4.2.2.4-13), and there were no changes suggesting saturation of metabolic capacity. Therefore, more than dose-proportional increases may be attributable to the saturation of efflux capacity in the small intestine.

In a study in dogs, the half-life was extended with the increasing oral dose. PMDA asked the applicant to explain whether or not such an extension was attributable to the elimination.

The applicant explained as follows:

Following single oral doses of 0.25, 0.5, and 1 mg/kg of mirabegron to dogs, the plasma mirabegron disappeared with the half-life of 4.4, 9.5, and 9.4 hours, respectively. At the dose of 0.25 mg/kg, the concentration was below the limit of quantitation in all animals at 24 hours post-dose, and the last time point where plasma mirabegron concentrations were quantifiable was at 12 hours post-dose in all animals. On the other hand, at the doses of 0.5 and 1 mg/kg, the plasma mirabegron concentrations were quantifiable at 24 hours post-dose in all animals. That is, the half-life at the dose of 0.25 mg/kg may have been underestimated due to the failure of capturing the elimination phase. The half-life of the plasma mirabegron concentration following a single oral administration was comparable between the doses of 0.5 and 1 mg/kg. In the dose range of

the concerned study, the half-life was not extended with the increasing dose. The applicant thus determined that effects on the elimination do not have to be considered.

PMDA has accepted the above explanation, but considers it necessary to pay attention to whether or not the pharmacokinetics of mirabegron in humans show nonlinear changes in the clinical dose range. Therefore, PMDA will continuously review this matter in the section for clinical data [see “4.(ii).B.(1) Pharmacokinetic nonlinearity of mirabegron”].

3.(ii).B.(2) Excretion of mirabegron into milk

Following administration of mirabegron to lactating rats, it was excreted into milk. The package insert proposed by the applicant includes the following caution statement; (i) animal studies have shown that mirabegron is excreted in milk, (ii) nursing mothers should discontinue breast-feeding while receiving mirabegron.

In terms of whether or not the caution proposed by the applicant is sufficient, PMDA considers as follows:

The study data in lactating rats treated with mirabegron (Attached document 4.2.2.5-1) show that (i) the mirabegron-derived radioactivity levels in milk were higher than those in plasma in dams at 1 and 4 hours post-dose, (ii) the plasma mirabegron concentration in dams was lower at 4 hours post-dose than 1 hour post-dose, while the mirabegron concentration in milk was higher at 4 hours post-dose than 1 hour post-dose, (iii) the radioactivity levels in the liver of suckling rats was higher at 24 hours post-dose than 4 hours post-dose. Based on the above findings, there is a concern about the effects of mirabegron excreted into milk on infants. Furthermore, in the toxicity study in rats, decreases in 4-day survival and body weight gain were observed in the offspring (Attached document 4.2.3.5.3-1). Although the offspring may have been adversely affected even before their birth due to intrauterine exposure of mirabegron, the possibility that these toxicological findings may be related to mirabegron-derived compounds excreted into milk cannot be ruled out in additional consideration of developmental delay in intrauterine fetuses observed following administration of mirabegron to dams. Taking into account that toxicological findings were observed in various organs such as the cardiovascular system in the toxicity studies of mirabegron, there remain concerns about whether only a general caution (prohibiting lactation) is sufficient for administration to nursing women. Mirabegron is a drug that alleviates symptoms of OAB and thus may be chronically used for an extended period to improve quality of life (QOL), and exposure of infants to the drug through breast milk seems to be inevitable. In consideration of these matters, a risk in infants outweighing benefit for the mothers cannot be ruled out, and it is appropriate to offer the other treatment options to nursing women wherever possible. Therefore, PMDA considers it important to include in the package insert not only general instructions on refraining from lactation but also detailed descriptions about risks potentially occurring in infants through their milk for giving caution. The appropriate precaution for nursing women will be finalized, taking account of comments raised in the Expert Discussion.

3.(ii).B.(3) Distribution of mirabegron into eye

Mirabegron-derived compounds were distributed into the eyes of pigmented rats at high concentrations and slowly eliminated. Concerning these findings, PMDA asked the applicant to explain the safety of mirabegron in clinical use.

The applicant explained as follows:

Following a single oral dose of 10 mg/kg of ¹⁴C-labeled mirabegron to pigmented male rats, M6, a phenethylamine metabolite of mirabegron, was distributed into the eyeballs at the highest level among mirabegron-derived compounds (unchanged compound and metabolites), followed by unchanged mirabegron (Attached document 4.2.2.3-4). Following a single oral administration of ¹⁴C-labeled mirabegron to cynomolgus monkeys, no M6 was detected in the plasma, and the radioactivity levels in the eyeballs at 168 hours post-dose was the third highest after the liver and

bile, but still approximately 6% in the eyeballs of pigmented rats treated with the single oral dose of 10 mg/kg of ^{14}C -labeled mirabegron (Attached document 4.2.2.2-6, 4.2.2.3-3). Based on the results, the applicant infers that the difference in radioactivity levels in the eyeballs between cynomolgus monkeys and pigmented rats is attributable to the difference in mirabegron's metabolite profile between animal species. The metabolite profile in humans was similar to that in cynomolgus monkeys; in Study CL-007 where a single dose of ^{14}C -labeled mirabegron 160 mg was administered orally under fasted conditions, no M6 was detected in the plasma. It has been known that binding of drugs to melanin is a common feature of basic drugs such as β -adrenoceptor antagonists and benzodiazepines (*Drug Metab Rev.* 1984;15:1183-212, *Regul Toxicol Pharmacol.* 1998;28:124-32). It has been reported that the ability of binding of drugs to eye melanin is not directly related to ocular toxicity (*Regul Toxicol Pharmacol.* 1998;28:124-32). Eye inflammation, scleral hyperemia, and conjunctival redness observed in the 2-week repeated oral dose toxicity study in dogs are attributable to the peripheral vasodilatation effect and considered as changes characteristic of dogs since it has been reported that β_3 -adrenoceptor stimulation leads to pronounced peripheral vasodilatation in dogs (*J Pharmacol Exp Ther.* 1996;278:1435-43). On the other hand, in the 26-week repeated oral dose toxicity study in rats (Attached document 4.2.3.2-3) and 52-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-11), ophthalmological examination and histopathological examination in the eye did not show changes related to administration of mirabegron. Based on the above, it is unlikely that the slow ocular elimination of mirabegron-derived compounds affects the eyes. In terms of the safety in human eyes, a visual acuity test and ophthalmoscopy were performed in a phase I single and multiple dose clinical study (Study CL-034) to investigate the effects of mirabegron on the eye. As a result, no clinically significant changes in visual acuity were noted. No abnormal fundal findings were noted in any subject. The incidence of adverse events classified into eye disorders (MedDRA/J Version 12.1 System Organ Class [SOC]) in the 3 Japanese clinical studies (Study CL-045, Study CL-048, and Study CL-051) was 0.7%, 1.4%, 1.7%, and 1.0% in the placebo, mirabegron 25 mg, 50 mg, and 100 mg groups, respectively. The incidences in the mirabegron groups were slightly higher than that in the placebo group, but the incidence did not show any dose-dependent increasing trend. The incidences of individual adverse events were also comparable between the placebo and the mirabegron groups. No glaucoma occurred. In the Japanese long-term treatment study (Study CL-051), the incidence of eye disorders was 5.3% in the 50 mg maintenance dose group and 10.0% in the 100 mg increased dose group. Adverse events reported by ≥ 2 subjects in each group were only asthenopia (3 subjects) in the 50 mg maintenance dose group and blepharitis (2 subjects) in the 100 mg increased dose group, and the other events occurred only in 1 subject. All of these events were mild in severity, and the long-term treatment did not increase their severity. No glaucoma occurred, either. In subjects with glaucoma in the 3 Japanese clinical studies (6 subjects in Study CL-045, 2 subjects in Study CL-048, 2 subjects in Study CL-051), preexisting glaucoma was not aggravated. Based on the above results, the applicant considers that clinical use of mirabegron is unlikely to cause safety issues in the eye.

PMDA considers as follows:

The non-clinical toxicity data and clinical data indicate that distribution of mirabegron-derived radioactivity into the eye, which was observed in a non-clinical pharmacokinetic study, is unlikely to become a clinically relevant problem. However, PMDA will continuously review the potential risk of glaucoma related to the pharmacologic action of mirabegron in the section for clinical data [see “4.(iii).B.(2).4) Effect on the eye”].

3.(iii) Summary of toxicology studies

3.(iii).A. Summary of the submitted data

Toxicity studies of mirabegron conducted include single dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproduction toxicity studies, local tolerance studies, skin sensitization studies, studies on impurities, and hemolytic potential studies.

3.(iii).A.(1) Single dose toxicity (Attached document 4.2.3.1-1, 4.2.3.1-2)

As single dose toxicity studies, an oral dose toxicity study in male and female F344 rats as well as male and female dogs were performed. The approximate lethal dose was determined to be 800 mg/kg in both male and female rats, 30 mg/kg in male dogs, and >30 mg/kg in female dogs. Treatment-related changes observed in rats included decreased locomotor activity, prone position, mydriasis, salivation, lacrimation, colored tear, clonic convulsion, stained fur, transient weight decrease, peripheral hepatocyte hypertrophy, and vascular degeneration. Treatment-related changes observed in dogs included red skin, increased heart rate, vomiting, recumbency, shallow breathing, and gasping respiration as well as focal dilatation of acinus, tissue destruction, and necrosis of the zygomatic gland.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in rats (2-, 13-, and 26-week oral dose as well as 2-week intravenous dose), dogs (2-week and 3-day oral dose), and cynomolgus monkeys (2-, 13-, and 52-week oral dose as well as 2-week intravenous dose). The major toxicological findings included effects on the cardiovascular system and the central nervous system (rats, dogs, cynomolgus monkeys), eye (rats, dogs), kidney (rats), salivary gland (dogs), and reproductive organs (rats).

Changes related to enhanced lipid metabolism and energy consumption through β_3 -adrenoceptors on adipocytes included smaller white adipocytes, and decreased and/or smaller lipid droplets in white and brown adipocytes in rats and cynomolgus monkeys even at low doses as well as decreased triglyceride in rats. The other changes in rats included increased food consumption, body weight fluctuation (mainly low weight), and lipofuscin deposition in the liver, cecum, bone marrow, etc.

The exposure (AUC_{24h}) at the no observed adverse effect level (NOAEL) determined in each repeat-dose toxicity study was compared with the exposure (AUC_{tau}) following multiple administration to foreign elderly subjects (aged ≥ 55 and ≤ 77 years) at the dose of 50 mg/day for 7 days in Study CL-072, the exposure to mirabegron at the NOAEL (3 mg/kg/day) in the 26-week repeated oral dose toxicity study in rats was 110 ng·h/mL in males and 113 ng·h/mL in females, which were 0.2 to 0.3 times the exposure in humans. The NOAEL in the 2-week repeated oral dose toxicity study in dogs was <1 mg/kg/day. The exposure to mirabegron at the dose of 1 mg/kg/day was 313 ng·h/mL in males and 269 ng·h/mL in females, which were 0.5 to 0.9 times the exposure in humans. The exposure to mirabegron at the NOAEL (10 mg/kg/day) in the 52-week repeated oral dose toxicity study in cynomolgus monkeys was 1267.35 ng·h/mL in males and 1091.94 ng·h/mL in females, which were 2.1 to 3.7 times the exposure in humans.

3.(iii).A.(2).1 Two-week repeated oral dose toxicity study in rats (Attached document 4.2.3.2-1)

Mirabegron (0 [vehicle], 10, 30, 100, 300 mg/kg/day) was administered orally to male and female F344 rats (n = 16/sex) for 2 weeks. Changes included increased alanine aminotransferase (ALT) in males and females, increased alkaline phosphatase (ALP) in females, and low triglyceride and increases in liver and kidney weights to body weight ratios in males in the ≥ 30 mg/kg/day groups, increased food consumption and water intake in males and females and reduced body weight gain in males in the 100 mg/kg/day group as well as decreased platelet count, increased plasma potassium level, and increased total excretion of sodium and chlorine into urine in males and females, increased ALP, total cholesterol, and phospholipid in males, and increased total excretion of potassium into urine, increased heart weight to body weight ratio, decreases in testis and vesicular gland actual weights or in testis and vesicular gland weights to body weight ratios in males, and increases in liver and kidney weights to body weight ratios in females in the ≥ 100

mg/kg/day groups. Changes observed in the 300 mg/kg/day group included decreased locomotor activity, reduced body weight gain, decreased food consumption, decreased reticulocyte percentage, increased urine protein, and decreased thymus actual weight and thymus weight to body weight ratio in males and females, lacrimation, ocular discharge, decreased hematocrit level, mean corpuscular volume (MCV), white blood cell count, and lymphocyte count, increased total cholesterol and phospholipid, increased total excretion of potassium into urine, decreased actual weight of the heart, decreases in spleen, ovary, and uterus actual weights and spleen, ovary, and uterus weights to body weight ratios, thymic atrophy, smaller/atrophy of uterus, and decreased hematopoiesis in the bone marrow in females. Changes in males in the same dose group included increased water intake, increased urine volume, decreased prostate actual weight and prostate weight to body weight ratio, smaller prostate and vesicular gland, and decreased vesicular gland secretory fluid. Even after the a 2-week withdrawal period, increases in heart and liver weights to body weight ratios were observed in males in the 300 mg/kg/day group, but the other changes observed during the treatment period resolved or showed a resolving trend during the withdrawal period. Based on the above, the NOAEL was determined to be 10 mg/kg/day in both males and females.

**3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study in rats
(Attached document 4.2.3.2-2)**

Mirabegron (0, 10, 30, 100, 300 mg/kg/day) was administered orally to male and female F344 rats (n = 10-16/sex) for 13 weeks. In Week 10 and Week 13, 2 females in the 300 mg/kg/day group died, and necropsy showed edema in the heart and lung. Changes observed in the ≥ 30 mg/kg/day groups included decreased platelet count, increased or increasing trend of plasma potassium level, decreased creatinine, and decreased zymogen granules in the parotid gland in males and females, salivation, reduced body weight gain, increased food consumption and water intake, decreased phospholipid (except for the 300 mg/kg/day group), and increased ALT in males, and lacrimation, and increased total excretion of chlorine into urine in females. Changes in males and females in the ≥ 100 mg/kg/day groups included increased ALP, decreased urine pH, positive reactions for urine protein and bilirubin, and deposition of lipofuscin in macrophage and Kupffer cells in the liver. Changes in males in the same dose groups included lacrimation, increased aspartate aminotransferase (AST), increased excretion of sodium and chlorine into urine, decreased percentage of α_1 -globulin fraction, and deposition of lipofuscin in macrophages in the bone marrow. Changes in females in the same dose groups included salivation, abdominal distention, increased food consumption, increased albumin concentration, and increases in liver and kidney actual weights or liver and kidney weights to body weight ratios, and decreased uterus actual weight and uterus weight to body weight ratio. Changes in males and females in the 300 mg/kg/day group included mandibular alopecia, increased percentage of albumin fraction, albumin/globulin ratio, and total cholesterol, decreased thymus actual weight and thymus weight to body weight ratio, decreased granular duct acidophil granules in the submandibular gland, hepatocyte swelling, deposition of lipofuscin in tubular epithelium in the kidney, deposition of lipofuscin and hemosiderin in lamina propria mucosae macrophages in the cecum, and thymic atrophy. Changes in males in the same dose group included mandibular stained fur, pale auricle, mydriasis, loose stool, clonic convulsion, respiratory distress, increased albumin concentration and total bilirubin, decreased white blood cell count, decreased monocyte percentage and blood glucose, bladder calculi, and necrosis and fibrillization of centrilobular hepatocytes in the liver. Changes in females in the same dose group included stained fur at and around the urinary tract and reproductive organs, reduced body weight gain, increased water intake, increased lymphocyte percentage, ALT, and phospholipid, decreased neutrophil percentage and percentage of α_1 -globulin fraction, decreased pituitary gland actual weight and pituitary gland weight to body weight ratio, deposition of lipofuscin in macrophages in the bone marrow, and uterine atrophy. Changes still observed following a 4-week withdrawal period included decreased phospholipid and total cholesterol, increased kidney actual weight or kidney weight to body weight ratio, decreased granular duct acidophil granules in the submandibular gland, decreased zymogen

granules in the parotid gland, deposition of lipofuscin in the liver, kidney, bone marrow, and cecum, and deposition of hemosiderin in the cecum in males and females, and reduced body weight gain in males. The other changes were reversible. Based on the above, the NOAEL was determined to be 10 mg/kg/day in both males and females.

3.(iii).A.(2).3) Twenty-six-week repeated oral dose toxicity study in rats
(Attached document 4.2.3.2-3, 4)

Mirabegron (0, 3, 10, 30, 100 mg/kg/day) was administered orally to male and female F344 rats (n = 12-18/sex) for 26 weeks. Changes observed in the ≥ 10 mg/kg/day groups included decreased creatinine in males and females, prone position, lacrimation, increased food consumption, decreased platelet count, increased plasma potassium level, and increased total excretion of potassium and chlorine into urine in males. Changes observed in the ≥ 30 mg/kg/day groups included salivation and eosinophilic hepatocytes in males and females, reduced body weight gain, increased water intake, increased hematocrit, hemoglobin, MCV, mean corpuscular hemoglobin (MCH), increased ALT, increased urine osmotic pressure, decreased urine pH, increased bilirubin, decreased actual weight of the thymus, and deposition of hemosiderin in the spleen in males, and prone position, increased food consumption, increased plasma potassium level, increased total excretion of chlorine into urine, and increased liver actual weight or liver weight to body weight ratio, and decreased zymogen granules in the parotid gland in females. Changes observed in the 100 mg/kg/day group included increased urine protein in males and females, increased total cholesterol, ALP, inorganic phosphate, total protein, albumin concentration, and β and γ -globulin concentration, decreased α_1 -globulin (concentration, fraction percentage), increased total excretion of sodium into urine, decreased urine volume, yellowish-brown urine, decreased actual weights of the brain and spleen, and decreased zymogen granules in the parotid gland in males. Changes in females in the same dose group included increased water intake, increased MCV, decreased platelet count and plasma chlorine level, decreased urine pH, increased bilirubin, and decreased thymus actual weight and thymus weight to body weight ratio. Following a 13-week withdrawal period, most of the changes were reversible except for decreased triglyceride. Based on the above, the NOAEL was determined to be 3 mg/kg/day in both males and females.

3.(iii).A.(2).4) Two-week repeated intravenous dose toxicity study in rats
(Attached document 4.2.3.2-6)

Mirabegron (0, 1, 3, 10 mg/kg/day) was administered orally to male and female F344 rats (n = 12/sex) for 2 weeks. Changes observed in the 10 mg/kg/day group included mydriasis, decreased locomotor activity, and prone position in males and females, and increased food consumption in females. Based on the above, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).5) Two-week repeated oral dose toxicity study in dogs
(Attached document 4.2.3.2-7)

Mirabegron (0, 1, 3, 10, 20 mg/kg/day) was administered orally to male and female dogs (n = 3-5/sex) for 2 weeks. Changes observed in the 20 mg/kg/day group included periocular swelling and ventricular tachycardia in males and females and eye inflammation in females. At the same dose, 1 of 5 females died, and all animals were necropsied until Day 7. Histopathological examination revealed left ventricular endocardial bleeding, left ventricular myocardial degeneration, and periportal vacuolation in the liver. One female in the 3 mg/kg/day group was necropsied on Day 6, because the administration could not be continued due to swelling of the eye, eyelid, and naso-oral part as well as exophthalmos. Changes observed in the ≥ 1 mg/kg/day groups included red skin, and degeneration and inflammation of the zygomatic gland in males and females, and periocular swelling in females. One female in the 3 mg/kg/day group was necropsied due to swelling of the eye, eyelid and naso-oral and exophthalmos on Day 6. Change observed in the ≥ 3 mg/kg/day groups included salivation in males and females, and vomiting and ocular discharge in females. Scleral congestion was observed in 1 each of males and females in the 3 mg/kg/day group. Changes observed in the ≥ 10 mg/kg/day groups included increased heart

rate, prolonged P wave and QRS interval, and elevation/increase in T wave in males and females, and vomiting and ocular discharge in males. Based on the above, the NOAEL was determined to be <1 mg/kg/day.

3.(iii).A.(2).6) Three-day repeated oral dose toxicity study in dogs (salivary gland toxicity study) (Attached document 4.2.3.2-8)

Mirabegron (20 mg/kg/day) was administered orally to female dogs (n = 14) for 3 days. Flush on the skin, palpebral conjunctivae, and oral mucosa, vomiting, decreased locomotor activity, fecal occult blood, salivation, pale palpebral conjunctivae, decreased food consumption, and mildly increased ALP and ALT were noted. Histopathological examination revealed atrophy and necrosis of acinar cells in the salivary gland (submandibular gland, major sublingual gland, minor sublingual gland, parotid gland, zygomatic gland), ductal dilatation, necrosis, detachment, hyperplasia and mineral deposition of ductal epithelium, interstitial edema, haemorrhage, thrombi, and cellular infiltration, and these changes were remarkable in the zygomatic gland. Following a 4- or 13-week withdrawal period, atrophy of acinar cells, and fibrillization and mineral deposition associated with ductal hyperplasia were observed, but their severity was reduced. Although peripheral hepatocyte hypertrophy, centrilobular and peripheral lipid droplet deposition, and increased centrilobular glycogen granules were observed in the liver, none of these changes were observed following a 13-week withdrawal period.

3.(iii).A.(2).7) Two-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-9)

Mirabegron (0, 10, 30, 60 mg/kg/day) was administered orally to male and female cynomolgus monkeys (n = 3-4/sex) for 2 weeks. On Day 1, ptosis and pale oral mucosa were observed in females in the 30 mg/kg/day group. Changes observed in the 60 mg/kg/day group included ptosis, decreased locomotor activity, recumbency, ventricular tachycardia, and prolonged PR and QRS intervals in males and females, and pale oral mucosa and prone position in males. Serious changes in clinical signs and ECG were observed in the 60 mg/kg/day group on Day 1, administration was terminated in 1 each of males and females after 2 days of treatment. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).8) Thirteen-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-10)

Mirabegron (0, 3, 10, 30 mg/kg/day) was administered orally to male and female cynomolgus monkeys (n = 3-5/sex) for 13 weeks. In males and females in the ≥ 10 mg/kg/day groups, prolonged or prolonging trend of PR interval were observed. In males in the 30 mg/kg group, a prolonging trend of QRS interval and ventricular tachycardia were observed. Findings observed during the administration period were reversible following a 4-week withdrawal period. Based on the above, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).9) Fifty-two-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-11)

Mirabegron (0, 3, 10, 30 mg/kg/day) was administered orally to male and female cynomolgus monkeys (n = 4/sex) for 52 weeks. Changes observed in the 30 mg/kg/day group included ptosis in males and females during the early phase of the administration, decreased locomotor activity, staggering gait, and pale oral mucosa in males, and prolonged or prolonging trend of PR, QRS, and QTc intervals in males and females. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).10) Single intravenous dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-12 [Reference data])

Mirabegron (0.1, 0.3, 1, 3, 10 mg/kg) was administered intravenously in a single dose to male and female cynomolgus monkeys (n = 2/sex) by the dose-titration method. Each group consisted

of 1 male and 1 female. In a male receiving 10 mg/kg, salivation, pale oral mucosa, and decreased locomotor activity occurred at approximately 2 minutes after the administration, followed by dyspnea, loss of pupillary reflex, mydriasis, and ventricular tachycardia, and died at 15 minutes. Therefore, administration to a female at the dose of 10 mg/kg was discontinued. In a male receiving 0.3 mg/kg, prolonged PR interval was observed at 6 minutes after the administration, and in a female receiving 3 mg/kg, prolonged PR and QRS intervals were observed. Necropsy showed red spots in cardiac papillary muscle in the dead male and 1 female which received all assigned doses, and histopathological examination revealed focal necrosis of the papillary muscle with macrophage infiltration in the heart in 1 female.

3.(iii).A.(2).11 Two-week repeated intravenous dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-13)

Mirabegron (0, 0.3, 1, 3 mg/kg/day) was administered intravenously to male and female cynomolgus monkeys (n = 3/sex) for 2 weeks. Prolonged PR interval and ventricular tachycardia were observed in males in the 1 mg/kg/day group. In the 3 mg/kg/day group, prolonged PR and QRS intervals and ventricular tachycardia were observed in males and females, and in 1 each of males and females, coma and slightly increased blood urea nitrogen, respectively, were observed on Day 3. Based on the above, the NOAEL was determined to be 0.3 mg/kg/day.

3.(iii).A.(3) Genotoxicity (Attached document 4.2.3.3.1-1 to 2, 4.2.3.3.2-1)

Genotoxicity tests of mirabegron conducted include bacterial reverse mutation test, chromosomal aberration test in mammalian culture cells (human peripheral blood lymphocytes), and micronucleus test in rats. In the chromosomal aberration test, increased counts of cells with chromosomal aberrations were observed following 3-hour treatment at the concentrations of 1280 µg/mL with metabolic activation and of 1255 µg/mL without metabolic activation at which mirabegron caused cytotoxicity. The other tests showed negative results.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1 Thirteen-week repeated oral dose toxicity study in mice (dose-finding study) (Attached document 4.2.3.4.1-2, 3 [Reference data])

To select the doses for carcinogenicity studies, mirabegron (0, 50, 100, 200 mg/kg/day) was administered orally to male and female B6C3F₁ mice (n = 12/sex) for 13 weeks. One female in the 200 mg/kg/day group and 2 males in the satellite group of the same dose group died on Day 43 and on Day 1, respectively. In the dead animals, decreased locomotor activity was observed following the first dose, but no other abnormalities were observed. Changes observed in the ≥50 mg/kg/day groups included increased body weight and food consumption, prone position, dark red foci in the glandular stomach, increased pigmentation in the Harderian gland, increased glycogen in hepatocytes in males and females, decreased vacuolation in cortical tubular epithelial cells in the kidney in males, and X zone regression in the adrenal gland, atrophy of acinar cells in the submandibular gland and parotid gland, and thymic atrophy in females. Increased extramedullary hematopoiesis in the spleen and thymic atrophy were observed in males in the ≥100 mg/kg/day groups. Changes observed in the 200 mg/kg/day group included hepatocyte centrilobular hypertrophy in males and females, and unicellular necrosis of acinar cells in the parotid gland in females. Based on the above, 100 mg/kg/day was selected as the highest dose in a carcinogenicity study.

3.(iii).A.(4).2 104-week oral dose carcinogenicity study in mice (Attached document 4.2.3.4.1-4)

Mirabegron (0, 25, 50, 100 mg/kg/day) was administered orally to male and female B6C3F₁ mice (n = 70/sex) for 104 weeks, but the frequency of tumorigenesis was not increased due to mirabegron. Thus, mirabegron was considered to have no carcinogenicity in mice.

3.(iii).A.(4).3 104-week oral dose carcinogenicity study in rats

(Attached document 4.2.3.4.1-5)

Mirabegron (0, 12.5, 25, 50 mg/kg/day) were administered orally to male F344 rats for 104 weeks and mirabegron (0, 25, 50, 100 mg/kg/day) to female F344 rats (n = 60/sex). Increased mortality was observed in females in the 100 mg/kg/day group. The frequency of tumorigenesis was not increased due to the administration of mirabegron. Thus, mirabegron was considered to have no carcinogenic potential in rats.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1 Study of fertility and early embryonic development to implantation in male rats (Attached document 4.2.3.5.1-1)

Mirabegron (0, 30, 100, 300 mg/kg/day) was administered orally to male SD rats (n = 20) from 2 weeks before mating to 4 weeks after mating. In all dose groups, decreased food consumption and reduced body weight gain were observed, but the food consumption was increased in the 30 and 100 mg/kg/day groups during the late phase of the administration. Tremor and decreased locomotor activity were observed in the 300 mg/kg/day group, and 14 of 20 rats died, resulting in a failure in evaluation. Mirabegron did not affect fertility and embryonic development in male rats. Based on the above, the NOAEL in paternal rats was determined to be <30 mg/kg/day for general toxicity and 100 mg/kg/day for reproductive performance and embryonic development.

3.(iii).A.(5).2 Study of fertility and early embryonic development to implantation in female rats (Attached document 4.2.3.5.1-2)

Mirabegron (0, 30, 100, 300 mg/kg/day) was administered orally to female SD rats (n = 20) from 14 days before mating to Gestation day 7. On Day 2, Day 10, and Day 19, 3 animals in the 300 mg/kg/day group died or were sacrificed moribund. Increased food consumption was observed in the 100 mg/kg/day group. Decreased locomotor activity, stained fur, lacrimation, tremor, decreased body weight and food consumption, prolonged diestrus, and decreases in corpora lutea count, implantation sites, and the number of live fetuses were noted in the 300 mg/kg/day group. Based on the above, the NOAEL in dams was determined to be 100 mg/kg/day for general toxicity and reproductive performance and 300 mg/kg/day for embryonic development.

3.(iii).A.(5).3 Rat embryo-fetal development study (dose-finding study) (Reference data) (Attached document 4.2.3.5.2-1)

Mirabegron (0, 30, 100, 300 mg/kg/day) was administered orally to pregnant SD rats (n = 10) from Gestation days 7 to 17. Tremor, decreased locomotor activity, and vaginal haemorrhage were noted in 3 animals in the 300 mg/kg/day group, and of them, 2 animals died. Increased placenta weight was observed in the 30 and 100 mg/kg/day groups, transiently decreased food consumption in the 100 mg/kg/day group, and decreased food consumption, body weight loss or reduced body weight gain in the 300 mg/kg/day group.

Changes in fetuses included increased or an increasing trend of wavy ribs, decreased ossification of sternbrae and sacrococcygeal vertebrae in the ≥ 100 mg/kg/day groups, and decreased fetal body weight, bent scapula, forearm bone, and humerus, and decreased ossification of metatarsal bones in the 300 mg/kg/day group.

3.(iii).A.(5).4 Rat embryo-fetal development study (Attached document 4.2.3.5.2-2)

Mirabegron (0, 10, 30, 100, 300 mg/kg/day) was administered orally to pregnant SD rats (n = 17-20) from Gestation days 7 to 17. In the 300 mg/kg/day group, 3 animals exhibited tremor, decreased locomotor activity, decreased respiratory rate, stained fur around the urethral opening or vaginal haemorrhage and died on Gestation days 9, 12, and 18. Necropsy showed a red lung. Although increased placenta weight was observed in the 30 and 100 mg/kg/day groups, no abnormal necropsy findings were noted, thus, this finding was not considered as a toxicity effect. In the ≥ 100 mg/kg/day groups, reduced body weight gain and decreased food consumption,

increased wavy ribs in fetuses, and decreased ossification of the metatarsal bones were observed. In the 300 mg/kg/day group, decreased fetal body weight, bent scapula, forearm bone, humerus, and ossa cruris, and decreased ossification of the sternbrae and sacrococcygeal vertebrae were noted. The skeletal examination on Postnatal day 4 in the 100 mg/kg/day group showed fused sternbrae and increased wavy ribs. Based on the above, the NOAEL in dams was determined to be 30 mg/kg/day for general toxicity, reproductive performance, and embryo-fetal development.

A pharmacokinetic study has demonstrated that mirabegron crosses the placenta and can be distributed into fetuses, and that it can be excreted into milk, resulting in its tissue distribution in the suckling rats [see “3.(ii).A.(4).4) Milk excretion”].

3.(iii).A.(5).5) Rats embryo-fetal development study (study for reversibility of wavy ribs) (Attached document 4.2.3.5.2-3)

Mirabegron (0, 100 mg/kg/day) was administered orally to pregnant SD rats (n = 39) from Gestation days 7 to 17. Reduced body weight gain, decreased food consumption, and increased placenta weight were observed in dams in the mirabegron groups. In fetuses in late pregnancy, increased wavy ribs, and decreased ossification of the sternbrae and left and right metacarpal bones were observed. Since no wavy ribs were found in Postnatal days 4 and 63, the applicant considers that the wavy ribs would resolve with development.

3.(iii).A.(5).6) Rabbit embryo-fetal development study (Attached document 4.2.3.5.2-5)

Mirabegron (0, 3, 10, 30 mg/kg/day) was administered orally to pregnant NZW rabbits (n = 17-22) from Gestation day 6 to 20. One rabbit in the 30 mg/kg/day group exhibited recumbency and dyspnea and died. In dams in the ≥ 10 mg/kg/day groups, decreased food consumption and fetal body weight were observed. In the 30 mg/kg/day group, decreased body weight or reduced body weight gain in dams, and increased post-implantation embryonic loss, as well as aortic dilatation, cardiomegaly, increased pulmonary accessory lobe loss, increased fused sternbrae, and decreased ossification progression in metacarpal bones and intermediate phalanges in forelimbs and hindlimbs (non-ossification) in fetuses were noted. Based on the above, the NOAEL was determined to be 3 mg/kg/day for general toxicity, reproduction, and embryo-fetal development in dams.

3.(iii).A.(5).7) Investigational study for fetal findings observed in the study for effects on embryo-fetal development in rabbits (effects of β_1 -adrenoceptor antagonist) (Attached document 4.2.3.5.2-6 [Reference data])

Pregnant NZW rabbits (n = 4-10) received mirabegron at the doses of 0 and 30 mg/kg/day and mirabegron at the dose of 30 mg/kg/day in combination with metoprolol, a β_1 -adrenoceptor antagonist, at the dose of 3 mg/kg/day from Gestation day 6 to 20. In dams in the mirabegron groups, reduced body weight and decreased food consumption were observed, and in those in the mirabegron + metoprolol group, a decreasing trend of food consumption was observed. Although increased frequencies of aortic dilatation and cardiomegaly were observed in fetuses in the mirabegron groups (74.3% and 30.8%, respectively), concomitant use of metoprolol decreased these frequencies (27.3% and 2.92%, respectively). The aortic dilatation and cardiomegaly observed in fetuses were suggested to be attributable to the β_1 -adrenoceptor agonistic effect of mirabegron.

3.(iii).A.(5).8) Study for effects on pre- and postnatal development, including maternal function, in rats (Attached document 4.2.3.5.3-1)

Mirabegron (0, 10, 30, and 100 mg/kg/day) was administered orally to pregnant SD rats (n = 19-20) from Gestation day 7 to Lactation day 20. On Gestation days 21 and 22, 2 dams in the 100 mg/kg/day group died.

In the ≥ 30 mg/kg/day groups, decreased food consumption was observed during the early pregnancy. In the 100 mg/kg/day group, reduced body weight gain was observed in dams, and decreased 4-day survival rate and reduced body weight gain were observed in offspring. Based on the above, the NOAEL was determined to be 10 mg/kg/day for general toxicity in dams, 100 mg/kg/day for reproductive functions, and 30 mg/kg/day for offspring.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1 Local tolerance (Attached document 4.2.3.6-1 to 3)

In the primary skin irritation test, a patch containing 0.5 g of mirabegron was applied to male JW rabbits (n = 3) for 4 hours. As a result, mirabegron was found to be non-irritant. In the ocular mucosa irritation test, mirabegron (100 mg) was administered to male JW rabbits (n = 3). As a result, mild irritation was observed, but in animals in which mirabegron was washed out at 30 second after application of the drug, the ocular mucosa irritation was alleviated. In the vascular local irritation test, mirabegron (10 mg/mL) was intravenously or perivenously administered to male JW rabbits (n = 3). As a result, mirabegron was found to be an irritant.

3.(iii).A.(6).2 Skin sensitization (Attached document 4.2.3.7.1-1, 2)

The Adjuvant and Patch test was conducted in male Hartley guinea pigs (n = 10) by treating animals with 1% and 10% mirabegron followed by induction of the sensitization reaction with 2% and 10% mirabegron. The positive rate on the mirabegron-induction site was 80% to 90%, and no skin reactions were observed on the vehicle-induction site. In animals sensitized with the vehicle, primary skin irritation occurred in response to mirabegron. In consideration of this reaction, the positive rate was calculated to be 50% to 60%, indicating that mirabegron have a moderate skin sensitization potential. Since the skin sensitization potential was indicated following the Adjuvant and Patch test, the Buehler test was conducted in male Hartley guinea pigs (n = 10) by treating animals with 1% and 10% mirabegron followed by induction of the sensitization reaction with 2% and 10% mirabegron. As a result, the positive rate was 40% to 50%, indicating moderate skin sensitization potential. In both tests, mirabegron caused primary skin irritation in animals sensitized with vehicle (liquid paraffin) followed by induction of the sensitization reaction with 2% and 10% mirabegron.

3.(iii).A.(6).3 Toxicity study on impurities (Attached document 4.2.3.7.6-1)

Mirabegron (0, 3, 10 mg/kg/day) containing impurity YM-181687 (acceptance limit, \leq ■%) at approximately 1% (measured value, 1.51%) was administered orally to male and female F344 rats (n = 10/sex) for 2 weeks. Smaller white adipocytes around the mesenteric lymph node in females in the ≥ 3 mg/kg/day groups, as well as increased food consumption in males and females, increased fibrinogen and β globulin ratio in males, and increased AST and ALT and, decreased triglyceride in females in the 10 mg/kg/day group. Based on the above, the NOAEL was determined to be 3 mg/kg/day in both males and females.

3.(iii).A.(6).4 Hemolysis test (Attached document 4.2.3.7.7-1)

An *in vitro* hemolysis test was performed using human blood. As a result, 10 mg/mL mirabegron dissolved in citrate buffer containing sucrose was found to be non-hemolytic.

3.(iii).A.(6).5 Study for effects on urine protein (Attached document 4.2.3.7.7-2 [Reference data])

An effect of mirabegron on the urine protein measurement system was investigated. Positive reactions were observed in multiple urine protein measurement systems including test papers (Multistix) used in repeated oral dose toxicity studies in rats. The positive reaction for urine protein observed in rats may be false due to an effect of mirabegron excreted into urine.

3.(iii).B. Outline of the review by PMDA

3.(iii).B.(1) Safety margin of mirabegron

It is in consideration that the exposure at the NOAEL determined in repeat-dose toxicity studies was below the clinical exposure in most of the repeat-dose toxicity studies in rats, dogs, and monkeys and that mirabegron is expected to be continued for an extended period, PMDA asked the applicant to explain the safety of mirabegron in clinical use.

The applicant responded as follows:

It has been known that dogs are highly sensitive to β -adrenoceptor stimulation; mirabegron increased the heart rate even at the extremely low dose (0.001 mg/kg, iv) and presented a pharmacologic action at another lower dose (0.0003 mg/kg, iv). In dogs, remarkable histopathological changes were observed in the zygomatic gland even at a low dose, but humans do not have a zygomatic gland. Based on the above, it is not appropriate to extrapolate the toxicity data in dogs to humans to assess the clinical safety of mirabegron. The changes in rats including prone position, salivation, increased AST and ALT, and increased total excretion of chlorine into urine, and prolonged PR interval in cynomolgus monkeys were observed only following the exposures exceeding that at the recommended clinical dose (50 mg), and these toxicological findings were reversible. In addition, the safety was confirmed at the doses up to 100 mg in the clinical long-term treatment study (Study CL-051).

PMDA considers as follows:

The applicant discusses that based on the exposure at the lowest observed adverse effect level (LOAEL), the toxicological findings in rats and cynomolgus monkeys were observed only after the exposure exceeding that at the recommended clinical dose. However, since the actual toxic dose is considered to be lower than the LOAEL determined based on the doses used in the toxicity studies, it is inappropriate that the safety margin was confirmed by data on the exposure at the LOAEL. Although the applicant's explanation that dogs are highly sensitive to β -adrenoceptor stimulation is understandable, some rats and cynomolgus monkeys died potentially from the effect on the heart, and also based on the toxicity data, a possibility that mirabegron may affected the heart in humans cannot be ruled out. The applicant claims that the clinical safety is supported by reversibility observed in many toxicological findings to some extent, but in consideration that mirabegron may be continuously administered for an extended period, the administration should be discontinued in clinical use when events related to the toxicological findings, which were found to be reversible in the toxicity studies, occur in humans. Based on the above, the applicant must consider setting actions for clinical use based on the toxicity profile of mirabegron, although the balance between risk and benefit of mirabegron should be determined based on the clinical data. The safety information about mirabegron is limited at present, and it is necessary to collect information via a post-marketing surveillance, taking the toxicity profile of mirabegron into account.

3.(iii).B.(2) Effects on reproductive organs

Mirabegron affected the steroid synthesis/metabolic pathway including lipid metabolism and then may affect the vesicular gland, prostate, uterus, adrenal gland, and ovary based on the following findings: (i) in the 2-week and 13-week repeated oral dose toxicity studies in rats, the sizes of the vesicular gland, prostate, and uterus were reduced to half of those in the control group at the high dose (300 mg/kg/day); (ii) in the 13-week repeated oral dose toxicity study in mice, X zone regression in the adrenal gland was observed in females; (iii) in the study of fertility and early embryonic development to implantation in rats, prolonged diestrus and decreased numbers of corpus lutea, implantations, and live fetuses were noted; and (iv) in the embryo-fetal development study in rabbits, increased post-implantation embryonic loss was noted. The above findings suggest that mirabegron may have affected the steroid biosynthesis and metabolism pathways, including lipid metabolism, resulting in the effects on the vesicular gland, prostate, uterus, adrenal gland, and ovary. PMDA asked the applicant to explain the clinical safety of mirabegron by discussing the mechanism of toxic effects, including the above mentioned potential effects of

mirabegron.

The applicant responded as follows:

In the repeated oral dose toxicity studies in rats, compared with those in the control group, the body weight in males and females in the high dose groups decreased by 10% and 8%, respectively, following 2-week administration of mirabegron, and in terms of weight of the accessory reproductive organs, the prostate, vesicular gland, and uterus weighed lower by 38%, 55%, and 56%, respectively. Following 13-week administration of mirabegron, the body weight in males and females decreased by 24% and 8%, respectively; and for weight of the accessory reproductive organs, the prostate, vesicular gland, and uterus weighed lower by 36%, 30%, and 67%, respectively. It has been reported that in male rats kept under limited feeding for 4 or 13 weeks, the organ weights of the prostate and vesicular gland decreased by 40% to 50% in association with the approximately 20% decrease in body weight (*Toxicology*. 1977;7:45-56, *Toxicol Appl Pharm*. 1979;47:15-22). For female rats, the Society of Toxicologic Pathology (STP) guideline describes that weight of the uterus often decreases in association with decreased body weight due to non-specific systemic toxicity (*Toxicol Pathol*. 2007;35:742-50). A non-protein feeding study shows that weights of the vesicular gland and prostate decreased, leading to a decrease in testosterone (*J Nutr Sci Vitaminol*. 1982;28:163-72). Furthermore, in toxicity studies of mirabegron, there were no histopathological findings clearly related to changes in sex hormone levels. Based on the above, atrophy of the accessory reproductive glands was a secondary consequence of reduced body weight gain.

As to X zone regression in the adrenal gland observed in female mice in the 13-week repeated oral dose toxicity study, necropsy revealed no effects on the reproductive organs and microvesiculation in subcutaneous adipocytes was observed in a dose-dependent manner. The results suggested that β_3 -adrenoceptor stimulation with mirabegron enhanced lipid metabolism, which then enhanced metabolism of lipids accumulated during the X zone regression process, further promoting regression of X zone cells. Therefore, X zone regression is unlikely to have been caused by direct effects of mirabegron on sex hormones.

The decreased numbers of implantations and live fetuses in the study of fertility and early embryonic development to implantation in female rats are considered to be changes related to decreased corpus luteum count associated with decreased ovulation since the pre- and post-implantation losses were not affected. Histopathological examination showed neither organic changes in the ovary and pituitary gland nor findings suggesting clear effects on the endocrine system. Prolonged diestrus, and decreased numbers of corpus lutea, implantations, and of live fetuses were inferred as a series of changes, and at the doses leading to these changes, decreased locomotor activity, reduced body weight gain, and decreased food consumption were observed as well. Therefore, these changes were considered attributable to the following sequence of changes associated with aggravated clinical observations, which leads to the secondary changes of the hypothalamus-anterior pituitary-ovary functions. Given that the study where affinities of mirabegron and its metabolites for various receptors were investigated (Attached document 4.2.1.1-5) showed little affinities of mirabegron and its metabolite for estrogen and testosterone receptors at 10 μ M, and in consideration of the chemical structure of mirabegron, it is unlikely to affect these receptors directly.

The post-implantation loss in rabbits is considered attributable to the β_1 -adrenoceptor agonistic effect of mirabegron since increased embryonic resorptions or fetal deaths were observed in a study for effects of Denopamine, which has a β_1 -adrenoceptor agonistic effect, on embryo-fetal development in rabbits as well. Since mirabegron is distributed into the fetuses via placenta, it may have directly affected the fetal cardiovascular system, leading to the post-implantation loss. However, it has been reported that the blood flow in the placenta was reduced following administration of isoproterenol, a β -adrenoceptor agonist, to rabbits (*Acta Obstetrica et*

Gynaecologica Japonica. 1983;35:1963-71), suggesting that the effect secondary to the reduced blood flow in the placenta may have been related to this finding.

Based on comparisons of the exposure (AUC_{24h}) at the NOAEL with that at the recommended clinical dose (50 mg), the safety margin was determined to be 11.7 to 25.0 times for atrophic changes in the reproductive organs in rats, 31.1 times for prolonged diestrus in rats, and 14.1 times for post-implantation loss in rabbits. As described above, changes observed in the toxicity studies were all related to aggravated clinical observations that resulted from the high exposures, and sufficient safety margins are found between toxic and clinical exposures. Therefore, similar findings are unlikely to occur in humans.

PMDA considers as follows:

The organ weights were remarkably decreased to approximately 40% to 60% of those in the control group in 2 weeks, while body weight gain was reduced by approximately 10%. Therefore, the applicant's claim that the size reductions of the vesicular gland, prostate, and uterus in rats were changes secondary to reduced body weight gain is unacceptable. In addition, although the applicant claims that findings in the study of fertility and early embryonic development to implantation in rats such as abnormal estrous cycle and decreased corpus luteum count are also changes secondary to reduced body weight gain, the applicant's claim is just speculation, which does not sufficiently account for these findings. In consideration that X zone regression in the adrenal gland was observed in mice, the possibility that mirabegron may affect the steroid synthesis and metabolism pathways including lipid metabolism cannot be ruled out.

At present, the mechanisms of the induction of findings in the toxicity studies remain unknown, and their effects on humans cannot be ruled out. Therefore, the applicant's claim that extrapolation into the effects on humans is low based only on the differences between the clinical exposure and those at toxic doses is insufficient. As described above, before clinical use of mirabegron, it is desirable to provide the information that changes in the reproductive organs and post-implantation loss were observed in toxicity studies and to avoid prescribing mirabegron to male and female patients in reproductive ages. The actions in response to changes in the reproductive organs observed in the toxicity studies will be reviewed, taking account of comments raised in the Expert Discussion.

Discussions on whether or not administration to pregnant women is acceptable will be continued in the next section.

3.(iii).B.(3) Effects on fetuses and offspring

In the studies for effects on embryo-fetal development, bent scapula and other bones, increased wavy ribs, and decreased ossification in the sternbrae in rats, increased fetal aortic dilatation and cardiomegaly and pulmonary accessory lobe loss in rabbits, and decreased metacarpal bones and intermediate phalanges in rats and rabbits were observed. PMDA thus asked the applicant to discuss the possible occurrence of similar findings in humans and safety margins for them and to explain whether or not relevant precautions have to be included in the package insert.

The applicant responded as follows:

Following administration of doxaminol, a β -adrenoceptor agonist, from Gestation day 8 to 16, wavy ribs occurred, while following administration from Gestation day 16 to 20, no wavy ribs occurred (*Teratology*. 1985;31:401-12). In addition, it has been reported that concomitant use of a β -adrenoceptor antagonist suppressed development of wavy ribs (*OyoYakuri*. 1984;27:239-49). Based on the above, development of wavy ribs is considered as a change attributable to the β -adrenoceptor agonistic effect of mirabegron. The study data of doxaminol suggest that exposure of the agonist after the organogenetic period will not lead to development of wavy ribs, and thus in the clinical settings, wavy ribs are unlikely to develop in human fetuses unless the exposure

occurs during the organogenetic period. Bent sites were found in fetal scapula as well as relatively large bones such as ribs and long bone, but were only local changes (curved or bent bones) without external abnormalities. These findings were likely to develop as a consequence of delayed ossification accompanied by uterine contraction during the late pregnancy. In rats treated with a chemical compound, which had a pharmacologic action different from that of mirabegron, bent bones were observed in fetuses but resolved at the time of weaning (in-house material, not submitted). Thus, the bent bones are probably reversible. The decreased ossification of sternbrae and sacrococcygeal vertebrae is considered to be a change associated with growth inhibition, which is indicated by the low fetal body weight, and may resolve with postnatal growth. In humans, the osteogenesis period is sufficiently separated from the time of uterine contraction, and skeletal abnormality is unlikely to occur. Even if delayed ossification occurs in humans, it will resolve during the fetal growth period until the delivery, because an additional study in rats (Attached document 4.2.3.5.2-3) has demonstrated that such change resolved with postnatal growth.

The aortic dilatation and cardiomegaly observed in rabbit fetuses were alleviated by concomitant use of a β_1 -adrenoceptor antagonist (Attached document 4.2.3.5.2-6), and it has been reported that xamoterol and prenalterol, both β_1 -adrenoceptor agonists, caused similar changes in rabbit fetuses, therefore, these changes are considered attributable to the β_1 -adrenoceptor agonistic effect of mirabegron. It has been reported that rabbit fetuses during the late organogenesis and development periods are highly susceptible to xamoterol, which can cause aortic dilatation and cardiomegaly, and it has been concluded in the discussion that these findings are functional changes but not consequences of the teratogenicity. In addition, since the incidence of the changes at 3 weeks postnatal was lower than that on Gestation day 29, it was discussed that these changes are reversible (*Jpn Pharmacol Ther.* 1988;16:1157-79). The pharmacokinetic profile of mirabegron in rabbits is different from those in humans and rats in that its metabolites, M5 and M16, are generated to a very large degree in rabbits. M5 has a β_1 -adrenoceptor agonistic effect equivalent to that of unchanged mirabegron, and the amount of M5 generated in rats, in which no aortic dilatation occurred in the fetuses, was approximately one tenth that in rabbits, thus possibly contributing to development of these findings. In humans, M5 is generated in a small amount and metabolized by multiple metabolic pathways, and therefore, the amount of M5 is unlikely to have large variability. These differences in pharmacokinetic profile among animal species suggest that rabbits are specifically susceptible to mirabegron. The applicant thus considers that the changes observed in rabbit fetuses are unlikely to occur in humans.

Although the incidence of pulmonary accessory lobe loss was 7.8% in the study for effects on embryo-fetal development in rabbits, this finding is frequently observed in rabbit fetuses, and actually the mean incidence of fetal pulmonary accessory lobe loss at the laboratory between 19 and 20 was 4.8% (range, 0.0%-13.5%). In addition, no correlation was found between the incidence of fetal pulmonary accessory lobe loss and the doses in the dose-finding study. Furthermore, there are no reports that pulmonary accessory lobe loss has occurred in rabbits following administration of denopamine and xamoterol, β_1 adrenaline agonists. The incidence of pulmonary accessory lobe loss in this study may have accidentally significantly differed from that in the control group (2.0%), due to this low incidence in the control group.

Concerning decreased metacarpal bones and intermediate phalanges in the fetuses, a skeletal examination was conducted using bone specimens stained with alizarin red S (simple stained bone specimen) in the study for effects on embryo-fetal development to inspect the ossified bones in terms of morphological and ossification aspects. This examination, however, cannot detect morphological abnormalities in non-stained parts. In the study for effects on embryo-fetal development, the metacarpal bone was partially unstained, but the cartilaginous part was confirmed, and thus the result was included in the study data as prematurely ossified bone but not loss. In addition, no morphological abnormalities were observed in limbs including phalanges,

and no fetus had any abnormal limb bones due to mirabegron.

Based on comparisons of the exposure (AUC_{24h}) at the NOAEL with that at the recommended clinical dose, the safety margin was determined to be 6.2 times for wavy ribs and 21.5 times for bent bones in rat fetuses as well as 14.1 times for aortic dilatation and cardiomegaly in rabbit fetuses.

Based on the above, the changes observed in the studies for effects on embryo-fetal development are unlikely to cause clinically relevant issues, and they may not have to be included in the package insert for precautions.

PMDA considers as follows:

Although the applicant discusses that the bent scapula in fetuses developed as a consequence of delayed ossification accompanied by uterine contraction during the late pregnancy, there is no literature supporting the applicant's claim that the uterine contraction can cause bent bones. The applicant's discussion cannot be justified. In addition, the applicant claims that the bent bones are reversible because in rats treated with a chemical compound, which had a pharmacologic action different from that of mirabegron, bent bones that had occurred in fetuses resolved at the time of weaning, and that the effect of mirabegron can be discussed based on the results from the study on the chemical compound. However, the basis for these discussions is unknown. Furthermore, the applicant claims that since these findings observed in fetuses in the reproductive and developmental toxicity studies were found reversible, the similar findings in human may be reversible if they occur. However, if the possibility of developmental delay such as low body weight and delayed ossification cannot be excluded in humans, this matter is critical. It is inappropriate to claim that the findings in fetuses are reversible and thus acceptable. In addition, the applicant discusses that the mirabegron metabolite, M5, is related to development of aortic dilatation and cardiomegaly observed in rabbit fetuses. However, PMDA cannot accept the applicant's logic that these changes are unlikely to develop in humans just because they were specific to rabbits in which the amount of M5 was greater than those in the other animals.

Most of the findings observed in the reproduction toxicity studies are related to the β -adrenoceptor agonistic effect of mirabegron as explained by the applicant, and the precautions about developmental delay and teratogenicity are included in the package insert for the other β -adrenoceptor agonists with greater safety margins than that of mirabegron. Based on the above, PMDA considers that the applicant should at least provide the same precautions. Furthermore, developmental delay such as low body weight and delayed ossification in fetuses due to mirabegron cannot be overlooked. Taking into account that mirabegron is a drug for QOL improvement by reducing OAB symptoms, the risk to the fetus may outweigh the benefit to the pregnant woman. In addition, considering that options for OAB treatment other than mirabegron and the above are available, the use of mirabegron in pregnant women should be contraindicated. PMDA will review whether or not the use of mirabegron in pregnant and lactating women is appropriate and what precautions are appropriate if it is not contraindicated, taking account of comments raised in the Expert Discussion.

The administration of mirabegron to lactating women will be discussed in the pharmacokinetics section (Attached document 4.2.2.5-1) [see "3.(ii).B.(2) Excretion of mirabegron into milk"].

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A. *Summary of the submitted data*

Although immediate-release (IR) formulations such as IR capsules and IR tablets were used in clinical studies during the early phase of development of mirabegron, oral controlled absorption

system (OCAS) tablet, an extended-release formulation, was later developed. Unless otherwise specified, the formulation of mirabegron used in clinical studies was in the OCAS tablet dosage form.

4.(i).A.(1) Concentration measurement method for biological samples

Since mirabegron is degraded by esterase in human plasma, sodium fluoride, an esterase inhibitor, was added to blood samples immediately after blood collection and mixed to measure plasma concentrations of mirabegron and its metabolites. The plasma and urine concentrations of mirabegron as well as those of its metabolites were determined by the validated LC-MS/MS method. The lower limit of quantitation of mirabegron differed depending on the study; it was 0.2 or 1 ng/mL for plasma samples and 2 or 10 ng/mL for urine samples. The lower limit of quantitation of mirabegron's metabolites was 0.5 or 1.0 ng/mL for plasma samples and 5 ng/mL for urine samples. Unless otherwise specified, pharmacokinetic parameters are expressed as mean \pm SD.

4.(i).A.(2) Bioequivalence

[REDACTED]. The to-be-marketed formulation of the mirabegron 50 mg tablet is the same as one used in Japanese phase II and III studies. For this application, the bioequivalence (BE) of mirabegron 25 mg tablets between the formulation for Japanese phase II studies and the to-be-marketed formulation as well as BE between the to-be-marketed formulations of the 25 mg tablet and 50 mg tablet were investigated.

4.(i).A.(2).1) BE between the formulation for Japanese phase II studies and to-be-marketed formulation
(Attached document 5.3.1.2-3, Evaluation data)

The level of formulation change for 25 mg tablets between the formulation for Japanese phase II studies and to-be-marketed formulation corresponded to the Level ■ specified in the “Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms” (PFSB/ELD Notification No. 1124004 dated November 24, 2006). Based on the results of the dissolution tests, both formulations were determined to be biologically equivalent.

4.(i).A.(2).2) BE between the to-be-marketed formulations with different strengths
(Attached document 5.3.1.2-4, Evaluation data)

The level of formulation change for the proposed product between the 25 mg tablets and 50 mg tablets corresponded to the Level ■ specified in the “Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms” (PFSB/ELD Notification No. 1124004 dated November 24, 2006). Based on the results of the dissolution tests, both formulations were determined to be biologically equivalent.

4.(i).A.(3) BA among formulations with different dissolution rates
(Attached document 5.3.1.3-1, Study CL-076, Study period April to July 2009, Evaluation data)

A 5-period cross-over study (including a washout period of ≥ 10 days) was conducted in foreign healthy adult subjects to investigate relative BAs of 3 formulations of mirabegron OCAS tablets with different dissolution rates (OCAS-H, OCAS-M [to-be-marketed formulation], and OCAS-L in decreasing order of the dissolution rate); MR-M formulation, which was OCAS-M tablets in a different batch/lot from that for the to-be-marketed formulation; and the formulation for intravenous infusion. Data from oral administration of OCAS-M tablets and intravenous administration of the formulation for intravenous infusion are presented as follows.

Following intravenous administration of mirabegron 7.5 mg over 120 minutes and single oral administration of mirabegron OCAS-M 25 mg tablets (17 male subjects, 12 female subjects), C_{\max} of mirabegron was 27.0 ± 4.90 and 9.8 ± 5.11 ng/mL, respectively, and AUC_{inf} was 133.8 ± 26.73 and 130.8 ± 58.75 ng·h/mL, respectively; the mean absolute BA of mirabegron OCAS-M tablets was 28.9%. Following intravenous administration of mirabegron 15 mg (16 male subjects, 14 female subjects) and oral administration of mirabegron OCAS-M 50 mg tablets (14 male subjects, 12 female subjects) to foreign healthy adult subjects, C_{\max} of mirabegron was 56.1 ± 11.64 and 22.9 ± 9.24 ng/mL, respectively, and AUC_{inf} was 287.7 ± 61.73 and 336.0 ± 130.80 ng·h/mL, respectively; the mean absolute BA of mirabegron OCAS-M 50 mg tablets was 35.4%. Following intravenous administration of mirabegron at the dose of 30 mg (18 male subjects, 12 female subjects) and oral administration of mirabegron OCAS-M 100 mg tablets (17 male subjects, 10 female subjects) to foreign healthy adult subjects, C_{\max} of mirabegron was 116.2 ± 20.22 and 77.4 ± 37.28 ng/mL, respectively, and AUC_{inf} was 561.9 ± 103.18 and 857.6 ± 378.64 ng·h/mL, respectively; the mean absolute BA of mirabegron OCAS-M 100 mg tablets was 45.0%. Following intravenous single doses of 7.5, 15 and 30 mg of mirabegron, CL_{tot} of mirabegron was 58.2 ± 11.22 , 54.3 ± 10.81 , and 55.1 ± 9.79 L/h, respectively, V_{ss} was 1763 ± 509.7 , 1643 ± 344.4 , and 1661 ± 441.2 L, respectively, and renal clearance (CL_{R}) was 14.35 ± 3.746 , 13.67 ± 3.562 , and 13.92 ± 2.910 L/h, respectively. At any intravenous dose, C_{\max} and AUC_{inf} in female subjects were approximately 20% and 27% higher than those in male subjects, respectively, CL_{tot} , V_{ss} , and CL_{R} in female subjects were lower than those in male subjects.

4.(i).A.(4) Absolute BA (Attached document 5.3.1.1-1, Study CL-033, Study period ■ to ■ 20■, Evaluation data)

A 2-treatment, 2-period cross-over study (including a washout period of ≥ 14 days) was conducted in 12 foreign healthy adult male subjects (n = 3 per group) to investigate the absolute BAs of single

oral administration of mirabegron 50 mg (to-be-marketed 50 mg tablet) + single intravenous administration of mirabegron 15 mg and single oral administration of mirabegron 150 mg (1 tablet each of 100 mg tablets and to-be-marketed 50 mg tablets) + single intravenous administration of mirabegron 50 mg. Following single oral administration of mirabegron 50 mg, C_{max} and AUC_{inf} of mirabegron were 18.2 ± 6.8 ng/mL and 225 ± 97 ng·h/mL, respectively, while following intravenous administration of mirabegron 15 mg at an increasing infusion rate over 120 minutes, C_{max} and AUC_{inf} of mirabegron were 78.8 ± 14.6 ng/mL and 230 ± 49 ng·h/mL, respectively, the mean absolute BA was 24.3%. Following single oral administration of mirabegron 150 mg, C_{max} and AUC_{inf} of mirabegron were 160 ± 67 ng/mL and 1176 ± 469 ng·h/mL, respectively, while following intravenous administration of mirabegron 50 mg at an increasing infusion rate over 120 minutes, C_{max} and AUC_{inf} were 278 ± 46 ng/mL and 839 ± 135 ng·h/mL, respectively, the mean absolute BA was 45.2%. Following intravenous administration of mirabegron 15 mg, CL_{tot} and V_{ss} were 67.3 ± 16.1 L/h and 1606 ± 427 L, respectively, while following intravenous administration of mirabegron 50 mg, CL_{tot} and V_{ss} were 60.8 ± 9.2 L/h and 1473 ± 406 L, respectively. Following intravenous administration of mirabegron 15 mg, the urine excretion rate of unchanged mirabegron from time 0 to the last measurable time point ($Ae_{last}\%$) and CL_R were $19.3\% \pm 2.6\%$ and 15.8 ± 3.9 L/h, respectively, while following intravenous administration of mirabegron 50 mg, $Ae_{last}\%$ and CL_R were $24.0\% \pm 1.8\%$ and 16.4 ± 2.9 L/h, respectively.

4.(i).A.(5) Japanese clinical studies for food effects

4.(i).A.(5).(a) Study CL-064 (Attached document 5.3.1.1-2, Evaluation data)

A 2-treatment, 2-period cross-over study (including a washout period of ≥ 12 days) was conducted in 24 Japanese healthy adult subjects ($n = 12$ per group, but 1 subject discontinued the study) using the to-be-marketed formulation to investigate food effects on pharmacokinetics of mirabegron. Following single oral administration of mirabegron 50 mg tablets to subjects in the fasted state or within 10 minutes after a high-fat diet, t_{max} of mirabegron was 3.5 ± 0.9 and 4.7 ± 1.5 hours, respectively, C_{max} was 29.40 ± 23.79 and 10.28 ± 6.19 ng/mL, respectively, the area under the plasma concentration-time curve from time 0 to the time of last measurement (AUC_{last}) was 214.91 ± 105.50 and 100.96 ± 31.51 ng·h/mL, respectively; and $t_{1/2}$ was 28.1 ± 3.3 and 30.7 ± 4.6 hours, respectively. The geometric mean ratios of C_{max} and AUC_{last} following administration of a high-fat diet to that following fasted administration were 0.389 and 0.504, respectively.

4.(i).A.(5).(b) Study CL-078 (Attached document 5.3.1.1-3, Evaluation data)

A 6-treatment, 3-period cross-over study (including a washout period of ≥ 12 days) was conducted in 72 Japanese healthy adult subjects (12 subjects per group, but 1 subject each in the 50 and 100 mg groups discontinued the study) using the to-be-marketed 50 mg tablets to evaluate food effects on pharmacokinetics of single doses of 50 mg and 100 mg of mirabegron in the fasted state, after a regular meal, and after a high-fat diet. The pharmacokinetic parameters of mirabegron in plasma following administration in the fasted state, after a regular meal, and after a high-fat diet by sex are as shown in the table below.

Based on combined plasma concentration data of both male and female subjects, the geometric mean ratios of C_{max} following administration of mirabegron 50 mg after a regular meal and after a high-fat diet to that following fasted administration were 0.342 and 0.474, respectively, and the ratios for AUC_{last} were 0.467 and 0.679, respectively. In addition, the geometric mean ratios of C_{max} following administration of mirabegron 100 mg after a normal meal and after a high-fat diet to that in the fasted state were 0.357 and 0.514, respectively, and the ratios for AUC_{last} were 0.488 and 0.715, respectively.

Table. Pharmacokinetic parameters of mirabegron in plasma following administration in the fasted state, after a regular meal, and after a high-fat diet by sex

		Male subjects			Female subjects		
		In the fasted state n = 18	After a normal meal n = 18	After a high-fat diet n = 18	In the fasted state n = 17	After a normal meal n = 17	After a high-fat diet n = 17
Mirabegron 50 mg	t _{max}	3.39 ± 0.98	4.72 ± 1.64	4.61 ± 1.29	3.71 ± 1.41	5.06 ± 0.97	5.24 ± 1.52
	C _{max}	28.63 ± 17.31	8.72 ± 7.68	14.68 ± 10.40	42.51 ± 38.44	18.35 ± 14.35	18.04 ± 11.14
	AUC _{last}	283.95 ± 105.32	130.72 ± 56.45	200.88 ± 76.94	379.69 ± 145.86	187.07 ± 83.95	245.15 ± 81.80
	t _{1/2}	39.1 ± 6.7	40.9 ± 9.6	42.0 ± 6.6	40.7 ± 10.1	46.1 ± 17.6	45.5 ± 10.7
Mirabegron 100 mg	t _{max}	3.44 ± 0.98	4.95 ± 1.39	5.67 ± 1.46	3.71 ± 1.10	5.71 ± 0.77	5.59 ± 1.94
	C _{max}	89.60 ± 57.62	27.74 ± 21.47	49.38 ± 24.56	117.78 ± 54.61	58.87 ± 40.36	55.41 ± 31.87
	AUC _{last}	670.64 ± 241.74	297.46 ± 123.78	497.41 ± 139.26	1021.72 ± 288.03	573.50 ± 189.37	687.58 ± 196.87
	t _{1/2}	34.0 ± 4.9	34.5 ± 7.1	33.7 ± 5.6	38.6 ± 7.5	39.9 ± 12.3	37.7 ± 7.6

Mean ± SD

AUC_{last}: ng·h/mL, C_{max}: ng/mL, t_{max} and t_{1/2}: hours

4.(i).B. Outline of the review by PMDA

Food effect studies in Japanese healthy adult subjects (Study CL-064, Study CL-078) showed that C_{max} and AUC of mirabegron administered in the fasted state were approximately 2 times higher than those after a meal. Therefore, PMDA asked the applicant to discuss providing cautions about food effects on pharmacokinetics of mirabegron.

The applicant responded as follows:

According to data from Study CL-078, C_{max} following administration of mirabegron 50 mg in the fasted state did not exceed that following administration of mirabegron 100 mg after a normal meal, and AUC_{inf} following administration of mirabegron 50 mg in the fasted state did not exceed that following administration of mirabegron 100 mg after a normal meal [see the table in “4.(i).A.(5).(b) Study CL-078”]. In a Japanese phase II study (Study CL-045), the incidence of adverse events at mirabegron 100 mg was higher than that at 50 mg, but most of them were mild in severity. In a Japanese long-term treatment study (Study CL-051), there was no marked increase in the incidence of adverse events associated with the mirabegron dose increased to 100 mg or extended treatment period. Data from both studies have demonstrated that there are no safety concerns with ≤100 mg mirabegron. Therefore, it is unnecessary to provide precautions about food effects on pharmacokinetics of mirabegron.

PMDA considers as follows:

Although the dosage and administration of mirabegron stipulate that the drug should be administered after a meal, it is important to state explicitly that the plasma concentration of mirabegron following fasted administration may be approximately twice higher than that after a meal. To provide explicit cautions about the risk following fasted administration, the applicant should provide the information that administration of mirabegron in the fasted state results in high plasma concentrations, but not the applicant’s proposed information that administration after a meal results in low plasma concentrations.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A. Summary of the submitted data

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1 Plasma protein binding and distribution in blood cells

(a) Plasma protein binding (Attached document 4.2.2.3-1, 5.3.2.1-1, 5.3.2.1-2)

¹⁴C-labeled mirabegron was added to plasma from Japanese and Caucasian healthy adult male subjects to obtain a final concentration of 200 to 5000 ng/mL. The plasma protein binding rate of mirabegron was 76.3% to 76.9% in Japanese subjects and 72.2% to 73.3% in Caucasian subjects. ¹⁴C-labeled mirabegron was added to solutions containing human serum albumin (40 mg/mL), human α_1 -acid glycoprotein (1 mg/mL), low-density lipoprotein (LDL) (3 mg/mL), high-density lipoprotein (HDL) (3 mg/mL), or human γ -globulin (10 mg/mL), which were prepared based on these plasma protein concentrations in healthy adult subjects, to obtain a final concentration of 200 to 5000 ng/mL. The plasma protein binding rate of mirabegron was 33.9% to 37.4% with human serum albumin, 24.0% to 31.6% with human α_1 -acid glycoprotein, 9.9% to 15.3% with LDL, 4.2% to 11.9% with HDL, and 2.1% to 5.0% with human γ -globulin.

M5 (metabolite generated following hydrolysis of the amide bond and acetyl conjugation on the amine group in mirabegron) and M16 (deacylated metabolite of mirabegron) were added to plasma from Japanese and Caucasian healthy adult male subjects to obtain a final concentration of 10 to 250 ng/mL. The plasma protein binding rate of M5 was 64.5% to 67.1% in Japanese subjects and 44.4% to 47.2% in Caucasian subjects, and that of M16 was 47.4% to 48.5% in Japanese subjects and 32.4% to 33.7% in Caucasian subjects.

(b) Distribution in blood cells (Attached document 4.2.2.3-2)

¹⁴C-labeled mirabegron was added to human blood to obtain a final concentration of 100 to 2500 ng/mL, and the mixtures were incubated at 37°C for 30 minutes. The ratio of blood to plasma radioactivity levels was 1.41 to 1.43.

4.(ii).A.(1).2 *In vitro* metabolism

(a) CYP-mediated metabolism (Attached document 4.2.2.4-2, 5.3.2.2-1)

¹⁴C-labeled mirabegron was added to human liver microsome to obtain a final concentration of 10 μ M and the mixture was incubated with and without NADPH at 37°C for 60 minutes. In an HPLC chromatogram of the sample with NADPH, ≥ 3 metabolite peaks were detected, while in a chromatogram of that without NADPH, no metabolite peaks were detected.

Mirabegron was added to the expression systems of human cytochrome P450 (CYP) isoforms, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5, to obtain a final concentration of 0.2 μ M, followed by incubation with NADPH at 37°C for 45 minutes. Among the CYP isoforms, CYP2D6 exhibited the highest metabolic activity, followed by CYP3A4.

Mirabegron was added to human liver microsome to obtain a final concentration of 0.2 μ M, and then ketoconazole (CYP3A4 inhibitor) was added at final concentrations of 0.01 to 1 μ M or troleandomycin (CYP3A4 inhibitor) was added at final concentrations of 1 to 100 μ M. The mixture was then incubated at 37°C for 45 minutes. The metabolism of mirabegron was inhibited by 52% and 20% by ketoconazole at 1 μ M and troleandomycin at 100 μ M, respectively. Mirabegron was added to human liver microsome preincubated with anti-CYP3A4 serum at room temperature for 30 minutes, or with anti-CYP2D6 antibody on ice for 20 minutes, to obtain a final concentration of 0.2 μ M, followed by incubation with NADPH at 37°C for 45 minutes. The metabolism of mirabegron was inhibited by up to 80% and up to 10% by anti-CYP3A4 serum and anti-CYP2D6 antibody, respectively.

(b) Esterase-mediated metabolism (Attached document 5.3.2.3-4, 5.3.2.3-5)

¹⁴C-labeled mirabegron was added to human plasma to obtain a final concentration of 100 ng/mL followed by incubation at 37°C for 120 minutes. As a result, M16 was observed.

Mirabegron was added to each of human blood, plasma, liver microsome, small intestine microsome, liver S9, small intestine S9, acetylcholinesterase (recombinant) expression system, butyrylcholinesterase (BuChE) purified from human serum as well as carboxylesterase (CE) 1 and 2 expression systems to obtain a final concentration of 5 µM and the mixture was incubated for 15 to 60 minutes. Mirabegron was metabolized into M16 in the presence of human blood, plasma, and BuChE, and their Michaelis constant (K_m) of the substrate drug estimated from the formation rate of M16 was 14.5, 15.2, and 13.4 µM, respectively.

Inhibitory effects of various esterase inhibitors against metabolism of mirabegron into M16 by human blood, plasma, and BuChE purified from human serum were investigated. The metabolism of mirabegron into M16 by human blood, plasma, and BuChE purified from human serum was inhibited in the presence of BuChE inhibitors, such as phenylmethylsulfonyl fluoride at 0.1 mM, eserine at 0.01 mM, diisopropylfluorophosphate at 0.01 mM, and ethopropazine at 0.01 mM, by ≥90% of the metabolism in the absence of inhibitors. In the presence of 1,5-bis(4-allyldimethylammoniumphenyl) pentane-3-one dibromide at 0.1 mM, an acetylcholinesterase inhibitor, the metabolism into M16 was inhibited by approximately 60% to 70% of that in the absence of inhibitors. On the other hand, the metabolism was hardly inhibited in the presence of 5,5'-dithiobis(2-nitrobenzoate) and ethylenediaminetetraacetic acid, a paraoxonase/arylesterase inhibitor, as well as bis-p-nitrophenylphosphate, a CE inhibitor.

4.(ii).A.(1).3) *In vitro* drug-drug interactions

**(a) Inhibitory effect of mirabegron against CYP metabolic activities
(Attached document 5.3.2.2-2, 5.3.2.2-5)**

The inhibitory effects of mirabegron at 0.114 to 250 µM (final concentration) against metabolisms of 3-Cyano-7-ethoxycoumarin for CYP1A2 and CYP2C19 expression systems, that of 7-Methoxy-4-(trifluoromethyl)-coumarin for CYP2C9 expression system, that of 3-[2-(*N,N*-diethyl-*N*-methylammonium)ethyl]-7-methoxy-4-methylcoumarin for CYP2D6 expression system, and that of 7-Benzoyloxy-4-(trifluoromethyl)-coumarin for CYP3A4 expression system were investigated. The most potent inhibitory effect of mirabegron was found against CYP2D6 (IC_{50} = 0.67 µM) among the CYP isoforms investigated, followed by CYP3A4 (IC_{50} = 42.5 µM) and CYP2C19 (IC_{50} = 227 µM), while the inhibitory effects against CYP1A2 and CYP2C9 were found to be weak (IC_{50} > 250 µM).

Dextromethorphan *O*-demethylation (CYP2D6 reaction) in human liver microsome with NADPH was inhibited in the presence of mirabegron 100 µM (final concentration) by 85.0% of the CYP2D6 reaction in the absence of mirabegron; and IC_{50} was calculated to be 13 µM. Following preincubation of mirabegron with human liver microsome in the presence of NADPH for 30 minutes, the concerned IC_{50} was decreased to 4.3 µM. Following preincubation of mirabegron at 3 µM (final concentration) with human liver microsome for 30 minutes, the CYP2D6 reaction was found at 28.0% of the control reaction (without mirabegron), but the CYP2D6 reaction of a 25-time diluted preincubation solution was found at 76.2% of the control reaction (without mirabegron). The IC_{50} values of mirabegron against phenacetin *O*-deethylation (CYP1A2), bupropion hydroxylation (CYP2B6), amodiaquine *N*-dealkylation (CYP2C8), diclofenac 4'-hydroxylation (CYP2C9), *S*-mephenytoin 4'-hydroxylation (CYP2C19), chlorzoxazone 6-hydroxylation (CYP2E1), testosterone 6β-hydroxylation (CYP3A4/5), and midazolam 1'-hydroxylation (CYP3A4/5) reactions were all >100 µM.

(b) Drug-drug interaction studies (Attached document 5.3.2.2-3, 5.3.2.2-4)

Effects of mirabegron on metabolisms of CYP2D6 and CYP3A4 substrates were investigated

using human liver microsome. As a result, the K_i values of mirabegron against metabolisms of dextromethorphan and metoprolol, CYP2D6 substrates, were 10.5 and 3.7 to 7.9 μM , respectively, and that of nifedipine, a CYP3A4 substrate, was 13.3 μM .

The IC_{50} values of ketoconazole and ritonavir against metabolism of mirabegron by human liver microsome were 0.47 and 0.065 μM , respectively.

(c) CYP induction of mirabegron (Attached document 5.3.2.2-6)

Following exposure of human hepatocytes in primary culture to mirabegron 10 μM for 3 days, the mRNA levels of CYP1A2 and CYP3A4 were found to be 1.82- and 1.13-fold those in the control group (without mirabegron), but mirabegron hardly affected phenacetin *O*-dealkylation (CYP1A2) and testosterone 6 β -hydroxylation (CYP3A4/5) activity.

4.(ii).A.(1).4 In vitro investigation of transporters

(a) P-glycoprotein (Attached document 5.3.2.3-6, 5.3.2.3-7)

The transport activity of ^{14}C -labeled mirabegron at 1 to 250 μM (final concentration) from basolateral to apical side via Caco-2 cells (human colonic adenocarcinoma-derived cell) was 4.1- to 9.0-fold that from apical to basolateral side. The basolateral to apical transport was almost completely inhibited by verapamil (P-glycoprotein inhibitor).

Mirabegron (16, 250 μM) did not affect the transport of ^3H -labeled vinblastine (P-glycoprotein substrate) from basolateral to apical side in MDCKII cells (canine kidney epithelial cells) forcibly expressing P-glycoprotein, but mirabegron at 250 μM increased the apical to basolateral transport 3.4 times.

(b) Organic cation transporter (Attached document 5.3.2.3-8, 5.3.2.3-9)

The cellular uptake of ^{14}C -labeled mirabegron at 10 μM (final concentration) into S2 cells (mouse proximal tubule-derived cells) forcibly expressing human organic cation transporter (OCT) 1, OCT2, and OCT3 was 1.3 to 2.0 times higher than that into S2 cells non-expressing OCT. The cellular uptake of ^{14}C -labeled mirabegron into human OCT1 and OCT3 expressing cells was saturated in a concentration range of 2 to 500 μM (final concentration), and the K_m values were 108 and 439 μM , respectively. The cellular uptake of ^{14}C -labeled mirabegron into OCT2 was not saturated in a mirabegron concentration range up to 500 μM . In any type of OCT expressing cells, imipramine and desipramine (OCT inhibitors) at 0.5 mM inhibited the cellular uptake by approximately $\geq 75\%$ of that in the absence of these inhibitors.

Mirabegron inhibited the cellular uptake of ^{14}C -labeled tetraethylammonium into human OCT1 expressing S2 cells, and IC_{50} was 47.2 μM . Mirabegron at 1 mM decreased the cellular uptake of tetraethylammonium into human OCT2 expressing cells by 44.2% compared with that without mirabegron.

(c) Studies using cryopreserved human hepatocytes (Attached document 5.3.2.3-10)

The cellular uptake of ^{14}C -labeled mirabegron at 1 μM (final concentration) into cryopreserved human hepatocytes was increased with increasing incubation time. The cellular uptake during incubation at 37°C was higher than that on ice. The cellular uptake of ^{14}C -labeled mirabegron at 1 μM (final concentration) into cryopreserved human hepatocytes was inhibited by cyclosporine A at 0.1 to 1 μM (organic anion transport polypeptide [OATP] inhibitor) as well as quinidine at 25 to 250 μM and 1-methyl-4-phenylpyridinium at 1 mM (OCT1 inhibitors) but the inhibition rate was $< 50\%$ of the cellular uptake without these inhibitors. Probenecid at 1 mM and prostaglandin $\text{F}_{2\alpha}$ at 30 μM (organic anion transporter 2 [OAT2] and OCT1 inhibitors), taurocholate at 1 mM (OATP and Na^+ -taurocholate cotransporting polypeptide [NTCP] inhibitor) as well as estradiol 17-glucuronide at 100 μM (OATP inhibitor) did not inhibit the cellular uptake of ^{14}C -labeled mirabegron into cryopreserved human hepatocytes.

4.(ii).A.(2) Pharmacokinetics in Japanese healthy adult subjects

4.(ii).A.(2).1 Phase I single and multiple dose study (Attached document 5.3.3.1-1, Study No. CL-034, Study period ■ 20■ to ■ 20■, Evaluation data)

Mirabegron (50, 100, 200, 300, 400 mg) was administered orally in a single dose of to 30 Japanese healthy adult male subjects (n = 6 per group) in the fasted state. The median t_{\max} of mirabegron was 3.5, 3.5, 2.0, 4.0, and 4.5 hours, respectively; C_{\max} was 31.01 ± 18.06 , 130.67 ± 43.79 , 164.51 ± 82.99 , 548.52 ± 92.50 , and 720.14 ± 264.40 ng/mL, respectively; AUC_{last} was 223.99 ± 78.96 , 773.02 ± 215.55 , 1251.58 ± 417.16 , 3053.27 ± 300.18 , and 3917.41 ± 694.76 ng·h/mL, respectively; and $t_{1/2}$ was 36.4 ± 11.8 , 30.8 ± 3.4 , 26.4 ± 3.6 , 25.1 ± 4.3 , and 23.9 ± 4.9 hours, respectively. CL_R of mirabegron calculated from plasma and urine mirabegron concentrations was 15.21 ± 1.85 , 9.91 ± 4.45 , 14.61 ± 1.96 , 14.29 ± 1.80 , and 12.14 ± 2.07 L/h, respectively, and the urine excretion rate from time 0 to 72 hours post-dose ($Ae_{72h}\%$) was $7.20\% \pm 2.32\%$, $7.61\% \pm 3.62\%$, $9.01\% \pm 2.66\%$, $14.57\% \pm 2.48\%$, and $11.81\% \pm 2.55\%$, respectively.

Mirabegron (100 and 200 mg) was administered orally in a single dose to 16 Japanese healthy adult male subjects (n = 8 per group) after breakfast followed by 2-day washout period, and then administered orally at the same doses for 7 days. In the mirabegron 100 mg group, the median t_{\max} on Day 1 (the first day of dosing) and Day 10 (Day 7 of multiple dosing) was both 5.0 hours; C_{\max} was 91.23 ± 42.00 and 136.14 ± 52.52 , respectively; AUC_{last} was 536.92 ± 112.36 and 1198.22 ± 190.01 ng·h/mL, respectively; $t_{1/2}$ was 28.8 ± 6.8 and 30.0 ± 4.4 hours, respectively; and CL_R was 14.80 ± 2.00 and 15.16 ± 2.11 L/h, respectively. In the mirabegron 200 mg group, the median t_{\max} on Day 1 and Day 10 was both 5.0 hours; C_{\max} was 313.08 ± 77.57 and 290.94 ± 90.64 ng/mL, respectively; AUC_{last} was 1471.14 ± 365.44 and 2663.41 ± 425.67 ng·h/mL, respectively; $t_{1/2}$ was 27.4 ± 7.7 and 28.0 ± 1.8 hours, respectively; and CL_R was 13.83 ± 2.78 and 13.00 ± 2.03 L/h, respectively.

4.(ii).A.(2).2 Single dose study with individual dose-escalation (Attached document 5.3.3.1-2, Study No. CL-066, Study period ■ to ■ 20■, Evaluation data)

Mirabegron (25, 50, and 100 mg) was administered orally in a single dose to 12 Japanese healthy adult male subjects in the fasted state in accordance with the individual dose-escalation procedure (with a washout period of ≥ 12 days). The median t_{\max} was 4.0, 3.0, and 3.0 hours, respectively; C_{\max} was 9.88 ± 3.91 , 30.10 ± 16.80 , and 80.45 ± 31.65 ng/mL, respectively; AUC_{last} was 85.56 ± 34.08 , 229.74 ± 81.25 , and 577.90 ± 192.95 ng·h/mL, respectively; and $t_{1/2}$ was 32.9 ± 7.8 , 31.9 ± 6.3 , and 28.6 ± 5.3 hours, respectively.

4.(ii).A.(3) Pharmacokinetics in foreign healthy adult subjects

4.(ii).A.(3).1 Mass balance study (Attached document 5.3.3.1-5, Study No. CL-007, Study period ■ to ■ 20■, Evaluation data)

^{14}C -labeled mirabegron (160 mg) was administered orally in a single dose to 4 foreign healthy adult male subjects. AUC_{inf} of total radioactivity in the plasma was $10,443 \pm 2328$ ng eq·h/mL and that of unchanged mirabegron in the plasma was 2285 ± 250 ng·h/mL. Of the radioactivity administered, 55.0% was excreted in urine and 34.2% in feces up to 408 hours post-dose (Day 17), while no radioactivity was detected in the exhaled air. The urine excretion rate (percentage of dose administered) of unchanged mirabegron was 25.0%.

As metabolites of mirabegron, M5, M8, M11, M12, M13, M14, M15, and M16 were identified in the plasma, and in the urine, M9 and M17 were identified in addition to the metabolites detected in the plasma. The mean urine excretion rates of unchanged mirabegron, M5, M8, M9, M11, M12 + M13, M15, M16, and M17 up to 48 hours post-dose were 18.4%, 2.9%, 1.3%, 0.6%, 3.2%, 1.4%, 0.6%, 1.7%, and 2.0% of the dose, respectively. In the feces, unchanged mirabegron was most abundantly detected, while the metabolites were hardly identified. The optical isomer of

mirabegron was not detected in the human plasma or urine.

4.(ii).A.(3).2) Multiple dose study on gender-related differences and in elderly (Attached document 5.3.3.1-7, Study No. CL-031, Study period [REDACTED] to [REDACTED] 20[REDACTED], Evaluation data)

Mirabegron (50, 100, 200, 300 mg) was administered orally in a single dose to 64 foreign healthy non-elderly subjects (18-55 years of age), and mirabegron (50, 200 mg) was administered orally in single a dose to 32 elderly subjects (65-77 years of age). Then, from 72 hours after the single oral dosing, mirabegron was administered orally once daily to the same subjects at the same dose as the first single one for 10 days. The pharmacokinetic parameters following the first and last doses are as shown in the table below.

Table. Pharmacokinetic parameters of mirabegron in non-elderly and elderly subjects following the first and multiple administration

		50 mg		100 mg		200 mg		300 mg	
Non-elderly subjects		Males n = 6	Females n = 6	Males n = 6	Females n = 6	Males n = 6	Females n = 6	Males n = 6	Females n = 6
After the first dose	AUC _{last}	185 ± 123	293 ± 170	500 ± 126	506 ± 156	1060 ± 500	1459 ± 476	1629 ± 623	2706 ± 940
	C _{max}	23.7 ± 12.1	40.1 ± 31.1	61.9 ± 17.0	78.6 ± 35.9	158 ± 76	200 ± 68	287 ± 170	461 ± 182
	t _{max}	3.50 ± 1.76	3.00 ± 0.89	3.00 ± 1.10	3.33 ± 1.03	2.68 ± 0.49	3.01 ± 0.89	3.00 ± 1.10	3.33 ± 0.82
	t _{1/2}	28.8 ± 5.7 ^{c)}	30.7 ± 4.3 ^{d)}	34.6 ± 8.9	32.5 ± 6.3	29.4 ± 4.9	31.4 ± 5.9	27.9 ± 4.6	27.6 ± 3.2
After the last dose	AUC _{24h}	262 ± 104	368 ± 180	519 ± 144	800 ± 294	1443 ± 406	2041 ± 1008	2473 ± 689	3888 ± 861
	C _{max}	32.8 ± 15.6	45.6 ± 26.5	72.0 ± 16.6	112 ± 65	220 ± 60	264 ± 155	381 ± 161	530 ± 183
	t _{max}	2.67 ± 1.51	3.33 ± 0.82	3.17 ± 0.75	3.33 ± 1.03	3.00 ± 1.26	3.67 ± 1.63	3.17 ± 1.17	3.67 ± 1.21
	t _{1/2}	36.7 ± 3.8	36.5 ± 8.6	36.8 ± 4.9	32.0 ± 3.2	32.7 ± 8.0	29.8 ± 6.9	29.2 ± 5.6	26.3 ± 6.5
Elderly subjects		Males n = 6	Females n = 6			Males n = 6	Females n = 6		
After the first dose	AUC _{last}	178 ± 61	209 ± 94			911 ± 371	1515 ± 474		
	C _{max}	34.2 ± 14.6	33.2 ± 17.8			150 ± 94	235 ± 110		
	t _{max}	4.33 ± 0.52	4.17 ± 1.17			3.67 ± 1.36	3.67 ± 0.82		
	t _{1/2}	30.3 ^{a)}	42.1 ± 8.5 ^{b)}			33.2 ± 4.9	35.5 ± 3.9		
After the last dose	AUC _{24h}	231 ± 77	274 ± 48			1464 ± 613	2114 ± 802		
	C _{max}	36.9 ± 15.0	36.5 ± 10.2			205 ± 134	290 ± 127		
	t _{max}	4.67 ± 0.82	4.01 ± 1.25			4.00 ± 0.90	3.51 ± 1.03		
	t _{1/2}	48.3 ± 10.2 ^{d)}	45.0 ± 12.6			35.5 ± 4.6 ^{d)}	34.9 ± 5.2		

Mean ± SD

AUC_{last} and AUC_{24h}: ng·h/mL, C_{max}: ng/mL, t_{max} and t_{1/2}: hours

a: n = 1, b: n = 3, c: n = 4, d: n = 5

4.(ii).A.(4) Pharmacokinetics in patients

4.(ii).A.(4).1 Japanese phase III studies (Attached document 5.3.5.1-2, Study No. CL-048, Study period July 2009 to ■ 2010, Evaluation data)

Mirabegron (50 mg) was administered orally once daily after breakfast in multiple doses to Japanese OAB patients, and plasma mirabegron concentrations at 18 to 30 hours post-dose at Week 12 or at the time of treatment discontinuation were measured. The geometric mean ratio of the concentration in female patients (193 patients) to that in male patients (33 patients) (females/males) was 1.349, and the ratio of the concentration in patients aged ≥ 65 years (93 patients) to that in patients aged < 65 years (133 patients) (≥ 65 years/ < 65 years) was 1.325. In addition, in terms of the plasma mirabegron concentrations at 2 to 6 hours post-dose at Week 4, Week 8 or Week 12, or at the time of treatment discontinuation, the geometric mean ratio of the concentration in female patients (274 patients) to that in male patients (46 patients) (females/males) was 1.340, and the ratio of the concentration in patients aged ≥ 65 years (132 patients) to that in patients aged < 65 years (188 patients) (≥ 65 years/ < 65 years) was 1.301.

4.(ii).A.(4).2 Population pharmacokinetic analysis (Attached document 5.3.5.3-1)

Population pharmacokinetic analysis was performed using plasma mirabegron concentration data consisting of 240 sampling points from 16 Japanese healthy adult male subjects who received multiple doses of mirabegron in a phase I study (Study CL-034) and 1686 sampling points from 588 Japanese OAB patients who received multiple doses of mirabegron in a phase II study (Study CL-045). In Study CL-034, mirabegron (100, 200 mg) was administered once daily after breakfast for 7 days, and the plasma concentration data on the last day of dosing were used in the analysis. In Study CL-045, mirabegron (25, 50, 100 mg) was administered orally once daily after breakfast, and the plasma concentration data at Week 4, Week 8, Week 12, or at the time of treatment discontinuation were collected and used in the analysis.

Distributions (median [minimum to maximum]) of the background factors deemed as potential covariates in Study CL-034 and Study CL-045, respectively, are as follows: age, 23.5 (20-29) and 57.0 (20-80) years; body height, 172.8 (163.4-184.4) and 156.7 (134.4-182.0) cm; body weight, 63.6 (56.3-75.8) and 55.0 (32.9-105.5) kg; Body Mass Index (BMI), 20.9 (19.5-23.9) and 22.2 (15.6-42.3) kg/m²; BSA, 1.74 (1.60-1.98) and 1.53 (1.17-2.04) m²; CRE 0.79 (0.64-0.91) and 0.60 (0.22-1.55) mg/dL; AST, 14.5 (12-19) and 21.0 (11-198) IU/L; ALT, 13.5 (6-24) and 18.0 (6-260) IU/L; TBL, 0.6 (0.5-1.2) and 0.6 (0.2-1.9) mg/dL; ALB, 4.5 (4.2-5.0) and 4.2 (3.2-5.9) g/dL; sex (males/females), 16 subjects/0 subject and 108 subjects/515 subjects; complications (presence/absence), 0 subject/16 subjects and 458 subjects/165 subjects; concomitant drugs (used/not used), 0 subject/16 subjects and 464 subjects/159 subjects; dose of 25 mg, 0 and 198 subjects; dose of 50 mg, 0 and 195 subjects; dose of 100 mg, 8 and 195 subjects; and dose of 200 mg, 8 and 0 subjects.

As the basic model of mirabegron pharmacokinetics, a 2-compartment model involving primary absorption process with a lag time (t_{lag}) based on the pharmacokinetics information in Study CL-034 was used. The plasma concentration showed a more than dos—proportional increase, thus, the basic model was set to be based on data from OAB patients in the 100 mg group and include relative BA (Fr), which differed depending on the dose and study, as a fixed effect. The inter-individual variability and intra-individual variability were set as proportional systematic error models.

As a result of covariate search, body height, total bilirubin, serum creatinine, and sex were selected as covariates in the final model for CL/F, and serum albumin and age were selected for Fr.

The obtained final model was as follows.

$$CL/F \text{ (L/h)} = 191 \times (HGHT/156.7)^{3.54} \times (TBL/0.6)^{-0.4} \times (CRE/0.6)^{-0.727} \times 0.676^{GEND} \times \exp(\eta_{CL})$$

$$V2/F \text{ (L)} = 1430$$

$$V3/F \text{ (L)} = 2880$$

$$Q/F \text{ (L/h)} = 172$$

$$Ka \text{ (h}^{-1}\text{)} = 0.404$$

$$t_{lag} \text{ (h)} = 0.783 \times \exp(\eta_{t_{lag}})$$

$$Fr = GRP \times (ALB/4.2)^{0.945} \times (AGE/57)^{0.357} \times \exp(\eta_{Fr})$$

$$Y_{ij} = C_{ij} \times (1 + \varepsilon_{ij})$$

CL/F: Apparent total body clearance

V2/F: Apparent distribution volume of the central compartment

Q/F: Apparent intercompartmental clearance

V3/F: Apparent distribution volume of peripheral compartment

Ka: Absorption rate constant

GRP: OAB patients in the 25 mg group, GRP = 0.365; OAB patients in the 50 mg group, GRP = 0.548; OAB patients in the 100 mg group, GRP = 1; healthy adult male subjects in the 100 mg group, GRP = 1.323; healthy adult male subjects in the 200 mg group, GRP = 1.413

HGHT: Body height, TBL: Total bilirubin, CRE: Serum creatinine

GEND: Sex (males, GEND = 0; females, GEND = 1), ALB: Serum albumin

AGE: Age (age ≤ 40 years was assumed to be AGE = 40)

Y_{ij} : Observed plasma concentration in individual j at ith measuring timepoint

C_{ij} : Predicted plasma concentration in individual j at ith measuring timepoint

η : Random variable that follows a Gaussian distribution with mean 0 and variance ω^2

ε : Random variable that follows a Gaussian distribution with mean 0 and variance σ^2

The inter-individual estimate of variance for CL (ω_{CL}^2) was 0.167 with the CV of 42.6%, the inter-individual estimate of variance for t_{lag} ($\omega_{t_{lag}}^2$) was 0.336 with the CV of 63.2%, and the inter-individual estimate of variance for Fr (ω_{Fr}^2) was 0.120 with the CV of 35.7%. The estimate of variance (σ_{re}^2) of the error variation was 0.332 with the CV of 62.8%.

4.(ii).A.(5) Studies on endogenous factors

4.(ii).A.(5).1 Study on gender-related differences and the elderly (Attached document 5.3.3.3-1, Study No. CL-072, Study period ■ to November 2009, Evaluation data)

In a 2-period cross-over study (including a washout period of ≥ 14 days), non-elderly (aged ≥ 19 and ≤ 45 years) foreign healthy subjects (18 males, 18 females) and elderly (aged ≥ 55 and ≤ 77 years) foreign healthy subjects (21 males, 18 females) received mirabegron (25, 50, 100 mg) orally twice daily in the fed state on Day 1, followed by multiple oral doses of mirabegron (25, 50, 100 mg) once daily after breakfast from Day 2 to Day 7. Each subject received mirabegron following 1 of 6 treatment sequences consisting of 2 of 3 dose levels in a 2-period cross-over manner. The pharmacokinetic parameters of mirabegron after the last dose in non-elderly male and female subjects and elderly male and female subjects are as shown in the table below.

Table. Pharmacokinetic parameters of mirabegron in non-elderly male and female subjects as well as elderly male and female subjects following multiple administrations

	25 mg		50 mg		100 mg	
	Males n = 11	Females n = 11	Males n = 12	Females n = 12	Males n = 12	Females n = 11
Non-elderly (≥19 and ≤45 years)						
AUC _{tau} (ng·h/mL)	165 ± 65	163 ± 46	413 ± 148	471 ± 88	947 ± 228	1366 ± 257
C _{max} (ng/mL)	21.6 ± 10.5	20.1 ± 5.6	54.4 ± 24.5	58.1 ± 15.8	134 ± 58	215 ± 60
t _{max} (h)	4.14 ± 0.84	3.86 ± 0.78	3.92 ± 0.87	4.58 ± 1.00	3.63 ± 1.11	4.00 ± 0.77
t _{1/2} (h)	54.3 ± 8.0	64.8 ± 7.9	58.3 ± 14.6	58.0 ± 8.0	54.1 ± 9.7	56.2 ± 8.0
Elderly (≥55 and ≤77 years)	Males n = 13	Females n = 12	Males n = 11	Females n = 11	Males n = 14	Females n = 11
AUC _{tau} (ng·h/mL)	113 ± 35	182 ± 56	341 ± 71	512 ± 178	992 ± 235	1682 ± 352
C _{max} (ng/mL)	11.7 ± 4.6	19.7 ± 5.6	43.5 ± 18.9	66.3 ± 27.3	130 ± 35	259 ± 81.8
t _{max} (h)	4.70 ± 0.85	3.88 ± 1.13	3.86 ± 1.31	4.45 ± 0.82	4.04 ± 1.10	4.05 ± 0.91
t _{1/2} (h)	64.7 ± 13.5	70.7 ± 12.5	59.7 ± 12.7	66.4 ± 14.4	58.2 ± 6.9	61.7 ± 7.0

Mean ± SD

The mean AUC_{tau} of each of the mirabegron metabolites after the last dose in non-elderly male and female subjects and elderly male and female subjects were as follows; the mean AUC_{tau} of M11 at 25 mg of mirabegron was 47.1, 51.0, 46.1, and 76.5 ng·h/mL, respectively; that at 50 mg was 121, 134, 150, and 201 ng·h/mL, respectively; and that at 100 mg was 296, 449, 423, and 709 ng·h/mL, respectively. The mean AUC_{tau} of M12 at 25 mg of mirabegron was 40.2, 27.5, 29.1, and 38.3 ng·h/mL, respectively; that at 50 mg was 115, 94.5, 82.9, and 98.5 ng·h/mL, respectively; and that at 100 mg was 255, 308, 286, and 414 ng·h/mL, respectively. The mean AUC_{tau} of M13 at 25 mg of mirabegron was 3.36, 3.17, 1.47, and 2.06 ng·h/mL, respectively; that at 50 mg was 11.5, 10.1, 10.1, and 12.9 ng·h/mL, respectively; and that at 100 mg was 35.3, 44.5, 45.8, and 64.7 ng·h/mL, respectively. The AUC_{tau} of M5, M8, M13, M14, M15, and M16 was < 10% of the total AUC_{tau} of unchanged mirabegron and its metabolites.

4.(ii).A.(5).2) Pharmacokinetic study in patients with renal impairment (Attached document 5.3.3.3-2, Study No. CL-038, Study period September 2008 to September 2009, Evaluation data)

Mirabegron (100 mg) was administered orally in a single dose in the fasted state to subjects with normal renal function (8 subjects) as well as subjects with mild renal impairment (eGFR, 60-89 mL/min/1.73 m², 8 subjects), subjects with moderate renal impairment (eGFR, 30-59 mL/min/1.73 m², 8 subjects), and subjects with severe renal impairment (eGFR, 15-29 mL/min/1.73 m², 8 subjects). The median t_{max} of unchanged mirabegron was 2.5, 4.0, 4.0, and 4.0 hours, respectively; C_{max} was 45.2 ± 26.9, 57.0 ± 50.0, 60.8 ± 42.0, and 93.8 ± 70.1 ng/mL, respectively; AUC_{inf} was 558 ± 249, 771 ± 480, 992 ± 512, and 1239 ± 654 ng·h/mL, respectively; t_{1/2} was 43.0 ± 6.47, 55.1 ± 13.58, 47.3 ± 10.88, and 52.1 ± 11.70 hours, respectively; and the plasma protein non-binding fraction was 0.32 ± 0.066, 0.29 ± 0.060, 0.27 ± 0.093, and 0.27 ± 0.039, respectively.

In subjects with normal renal function, subjects with mild renal impairment, subjects with moderate renal impairment, and subjects with severe renal impairment, AUC_{inf} of M11 was 216 ± 136, 274 ± 153, 631 ± 594, and 1466 ± 664 ng·h/mL, respectively, and AUC_{inf} of M12 was 201 ± 139, 269 ± 123, 629 ± 582, and 711 ± 665 ng·h/mL, respectively. The plasma concentrations of M14 and M8 were found to be greater especially in patients with severe renal impairment than in the other subjects. AUC_{inf} of M14 in subjects with normal renal function, subjects with mild renal impairment, subjects with moderate renal impairment, and subjects with severe renal impairment was 85 ± 32, 129 ± 72, 331 ± 243, and 672 ± 260 ng·h/mL, respectively, and AUC_{inf} of M8 was 15 ± 4.8, 39 ± 18, 31 ± 12, and 170 ± 205 ng·h/mL, respectively.

4.(ii).A.(5).3) Pharmacokinetic study in patients with hepatic impairment (Attached document 5.3.3.3-3, Study No. CL-039, Study period ■ 20■ to ■ 20■, Evaluation data)

Mirabegron (100 mg) was administered orally in a single dose to subjects in the following groups (n = 8 per group): (i) subjects with normal hepatic function who were comparable with patients with mild hepatic impairment the age, sex, and BMI (normal group A); (ii) patients with mild hepatic impairment (Child-Pugh score, 5-6); (iii) subjects with normal hepatic function who were comparable with patients with moderate hepatic impairment in terms of the age, sex, and BMI (normal group B); and (iv) patients with moderate hepatic impairment (Child-Pugh score, 7-9). The median t_{max} of unchanged mirabegron was 2.0, 3.0, 2.5, and 3.0 hours, respectively; C_{max} was 66.9 ± 74.4 , 71.9 ± 50.5 , 41.5 ± 31.8 , and 113 ± 68 ng/mL, respectively; AUC_{inf} was 615 ± 370 , 770 ± 391 , 486 ± 248 , and 784 ± 363 ng·h/mL, respectively; and $t_{1/2}$ was 56.7 ± 11.9 , 67.7 ± 14.9 , 55.4 ± 10.6 , and 51.2 ± 11.4 hours, respectively.

In the normal group A, group of patients with mild hepatic impairment, normal group B, and group of patients with moderate hepatic impairment, AUC_{last} of M11 was 199 ± 162 , 252 ± 146 , 160 ± 110 , and 160 ± 80 ng·h/mL, respectively, and AUC_{last} of M12 was 87.5 ± 55.4 , 224 ± 96 , 96.6 ± 67.5 , and 163 ± 116 ng·h/mL, respectively. The plasma concentrations of M5 and M13 were remarkably increased in patients with hepatic impairment. In the normal group A, group patients with mild hepatic impairment, normal group B, and group of patients with moderate hepatic impairment, AUC_{last} of M5 was 51.4 ± 72.2 , 161 ± 102 , 44.5 ± 44.7 , and 148 ± 90 ng·h/mL, respectively, and AUC_{last} of M13 was 8.70 ± 8.66 , 31.4 ± 14.4 , 7.21 ± 7.37 , and 38.6 ± 30.6 ng·h/mL, respectively.

4.(ii).A.(5).4) Study for CYP2D6 PM/EM (Attached document 5.3.3.4-4, Study No. CL-005, Study period ■ to ■ 20■, Evaluation data)

Mirabegron (160 mg [2 capsules of IR capsules 80 mg]) was administered orally in a single dose in the fasted state to 8 foreign healthy adult male subjects with CYP2D6 genotype and phenotype indicating poor metabolizer (PM) and 8 foreign healthy adult male subjects with the genotype and phenotype indicating extensive metabolizer (EM). C_{max} and AUC_{inf} in EM subjects were 230 ± 53 ng/mL and 1253 ± 153 ng·h/mL, respectively, and those in PM subjects were 263 ± 113 ng/mL and 1493 ± 394 ng·h/mL, respectively.

4.(ii).A.(6) Drug-drug interaction study

4.(ii).A.(6).1) Ketoconazole (Attached document 5.3.3.4-1, Study No. CL-036, Study period ■ to ■ 20■, Evaluation data)

Mirabegron (100 mg) was administered orally in a single dose to 23 foreign healthy adult subjects (12 males, 11 females) in the fasted state, followed by a ≥ 7 -day washout period, then multiple oral doses of 400 mg of ketoconazole once daily for 9 days plus a single dose of mirabegron (100 mg) concomitantly only on Day 4 of ketoconazole dosing, to investigate effects of concomitant use of ketoconazole on pharmacokinetics of mirabegron. The changes in plasma mirabegron concentration up to 24 hours post-dose are as shown in the figure below.

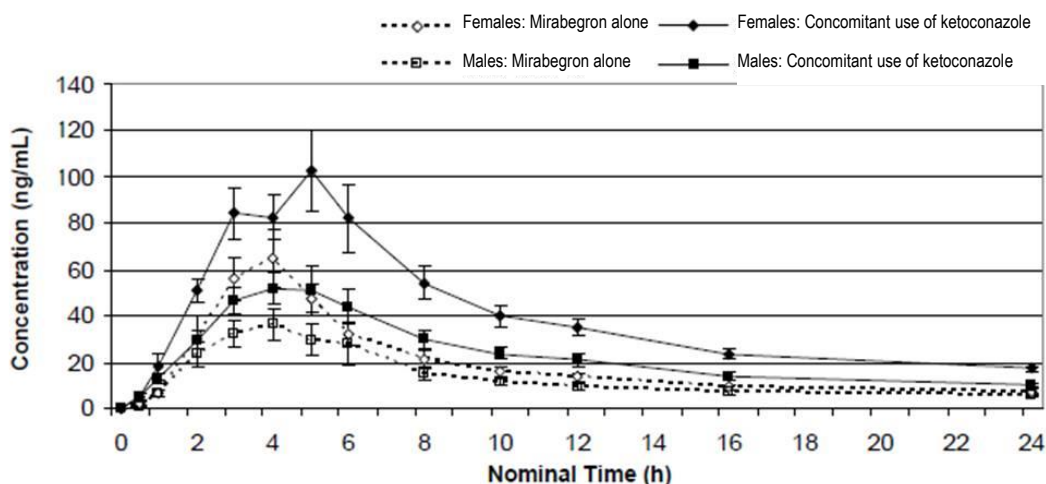


Figure. Changes in plasma mirabegron concentration until 24 hours post-dose (mean \pm SE)

The geometric mean ratios [90% CI] of C_{\max} and AUC_{\inf} of mirabegron in combination with ketoconazole to those of mirabegron alone were 1.45 [1.225-1.715] and 1.809 [1.626-2.012], respectively.

4.(ii).A.(6).2) Rifampicin (Attached document 5.3.3.4-2, Study No. CL-070, Study period October to ■ 2008, Evaluation data)

Mirabegron (100 mg) was administered orally in a single dose to 24 foreign healthy adult subjects (13 males, 11 females) in the fasted state on Day 1, followed by multiple oral doses of 600 mg of rifampicin once daily from Day 5 to Day 15 plus a single dose of mirabegron (100 mg) concomitantly on Day 12 of rifampicin dosing to investigate effects of concomitant use of rifampicin on pharmacokinetics of mirabegron.

The geometric mean ratios [90% CI] of C_{\max} and AUC_{\inf} of mirabegron in combination with rifampicin to those of mirabegron alone were 0.6531 [0.4982-0.8562] and 0.5645 [0.4907-0.6494], respectively.

4.(ii).A.(6).3) Warfarin (Attached document 5.3.3.4-3, Study No. CL-040, Study period ■ to ■ 2008, Evaluation data)

Warfarin (25 mg) was administered orally in a single dose to 24 foreign healthy adult subjects (n = 12/sex) on Day 1, followed by multiple oral doses of 100 mg of mirabegron once daily in the fasted state from Day 15 to Day 30 for 16 days plus a single dose of warfarin (25 mg) concomitantly on Day 23 to investigate effects of concomitant use of mirabegron on pharmacokinetic and pharmacodynamic parameters of warfarin.

Concomitant use of mirabegron did not affect C_{\max} and AUC_{\inf} of R- and S-warfarin as well as prothrombin time and international normalized ratio (INR).

4.(ii).A.(6).4) Metoprolol (Attached document 5.3.3.4-4, Study No. CL-005, Study period ■ to ■ 20■, Evaluation data)

Metoprolol (100 mg) was administered orally in a single dose to 12 foreign healthy adult male subjects with CYP2D6 genotype and phenotype indicating EM on Day 1, followed by multiple oral doses of 160 mg of mirabegron (two 80 mg IR capsules) once daily in the fasted state from Day 3 to Day 6 for 4 days plus a single dose of metoprolol (100 mg) concomitantly on Day 7 to

investigate effects of concomitant use of mirabegron on pharmacokinetics of metoprolol.

The geometric mean ratios [90% CI] of C_{\max} and AUC_{\inf} of metoprolol in combination with mirabegron to those of metoprolol alone were 1.897 [1.543-2.332] and 3.285 [2.699-3.998], respectively. C_{\max} and AUC_{\inf} of metoprolol were increased due to concomitant use of mirabegron. Following administration of metoprolol alone and concomitant use of metoprolol with mirabegron, C_{\max} of α -hydroxymetoprolol, a metoprolol metabolite generated by CYP2D6, was 81.7 ± 23 and 33.6 ± 17 ng/mL, respectively, and AUC_{last} of the metabolite was 540 ± 143 and 260 ± 127 ng·h/mL, respectively, which were decreased due to concomitant use of mirabegron.

4.(ii).A.(6).5) Desipramine (Attached document 5.3.3.4-5, Study No. CL-058, Study period ■ 20■ to ■ 20■, Evaluation data)

Desipramine was administered to 28 foreign healthy adult subjects ($n = 14/\text{sex}$) to investigate effects of concomitant use of mirabegron on pharmacokinetics of desipramine according to the following dosage regimen: a single oral dose of 50 mg of desipramine on Day 1, followed by multiple oral doses of 100 mg of mirabegron once daily in the fasted state from Day 5 to Day 23 plus a single dose of 50 mg of desipramine concomitantly on Day 18, then a 13-day washout period (Days 24-36), and then a single oral dose of 50 mg of desipramine on Day 38.

The geometric mean ratios [90% CI] of C_{\max} and AUC_{\inf} of desipramine in combination with mirabegron (Day 18) to those of desipramine alone (Day 1) were 1.79 [1.69-1.90] and 3.41 [3.07-3.80], respectively. The geometric mean ratios of C_{\max} and AUC_{\inf} in a single oral dose of 50 mg of desipramine after a washout (Day 38) to those of desipramine alone (Day 1) were 1.12 [1.05-1.20] and 1.13 [1.05-1.20], respectively.

4.(ii).A.(6).6) Digoxin (Attached document 5.3.3.4-6, Study No. CL-059, Study period ■ to ■ 20■, Evaluation data)

Digoxin (0.250 mg) was administered orally in a single dose to 23 foreign healthy adult subjects (11 males, 12 females) on Day 1, followed by multiple oral doses of 100 mg of mirabegron once daily in the fasted state from Day 10 to Day 23 plus a single dose of 0.250 mg of digoxin concomitantly on Day 18 to investigate effects of concomitant use of mirabegron on pharmacokinetics of digoxin.

The geometric mean ratios [90% CI] of C_{\max} and AUC_{last} of digoxin in combination with mirabegron to those of digoxin alone were 1.29 [1.17-1.42] and 1.27 [1.14-1.42], respectively.

4.(ii).A.(6).7) Metformin (Attached document 5.3.3.4-7, Study No. CL-006, Study period ■ to ■ 20■, Evaluation data)

To investigate effects of concomitant use of mirabegron on pharmacokinetics of metformin and those of concomitant use of metformin on pharmacokinetics of mirabegron, a study in foreign healthy adult male subjects was conducted and the subjects were assigned to the following 2 groups: (i) multiple oral doses of 160 mg of mirabegron (1 tablet of IR tablets 100 mg and 2 tablets of IR tablets 30 mg) once daily in the fasted state from Day 1 to Day 16, followed by mirabegron in combination with metformin 500 mg or placebo twice daily from Day 12 to Day 16 (on Day 16, administered only once in the morning) (Group A; 11 subjects in the concomitant use with metformin group, 4 subjects in the concomitant use with placebo group); and (ii) multiple oral doses of 500 mg of metformin twice daily from Day 1 to Day 16 (on Day 5 and Day 16, administered only once in the morning), followed by metformin in combination with mirabegron 160 mg or placebo from Day 6 to Day 16 (Group B; 12 subjects in the concomitant use with mirabegron group, 4 subjects in the concomitant use with placebo group).

The geometric mean ratios [90% CI] of C_{\max} and AUC_{24h} of mirabegron in combination with metformin to those of mirabegron alone were 0.79 [0.68-0.93] and 0.79 [0.70-0.90], respectively,

in Group A. The geometric mean ratios [90% CI] of C_{\max} and area under the plasma concentration-time curve from time 0 to 12 hours post-dose (AUC_{12h}) of metformin in combination with mirabegron to those of metformin alone were 0.90 [0.79-1.01] and 0.97 [0.87-1.08], respectively, in Group B.

4.(ii).A.(6).8) Oral contraceptives (Attached document 5.3.3.4-8, Study No. CL-068, Study period October 2008 to March 2009, Evaluation data)

A double blind, 2-treatment, 2-period cross-over study (including a washout period of 7 days) was conducted in 30 foreign healthy adult female subjects who had taken a combination oral contraceptive containing ethinyl estradiol (EE) and levonorgestrel (LNG) for ≥ 3 months (7 females discontinued the study). The subjects received a combination oral contraceptive (Minidril) containing 30 μg of EE and 150 μg of LNG orally once daily from Day 1 to Day 21 plus multiple oral doses of 100 mg of mirabegron in the fasted state concomitantly from Day 12 to Day 21 or the combination oral contraceptive orally once daily from Day 1 to Day 21 plus multiple oral doses of placebo concomitantly from Day 12 to Day 21.

There were no effects of concomitant use of mirabegron on C_{\max} and AUC_{τ} of EE and LNG.

4.(ii).A.(7) Pharmacodynamics

4.(ii).A.(7).1) Thorough QT/QTc study (Attached document 5.3.4.1-1, Study No. CL-037, Study period ■ to ■ 20■, Evaluation data)

In a 4-period cross-over study (including a washout period of ≥ 10 days), 48 foreign healthy adult subjects (25 males, 23 females) received multiple oral doses of 100 and 200 mg of mirabegron once daily in the fasted state for 7 days, and then a single oral dose of 400 mg of moxifloxacin (positive control) or placebo.

Following administration of mirabegron at doses of 100 and 200 mg on Day 7, t_{\max} (mean) of plasma mirabegron concentrations was 3.56 and 3.24 hours, respectively, C_{\max} was 110 ± 67 and 290 ± 108 ng/mL, respectively, and AUC_{τ} was 869 ± 383 and 2195 ± 687 ng·h/mL, respectively.

The primary endpoint was the difference from placebo in the mean changes in baseline-corrected QTcI interval. The values at the evaluation time points on Day 7 (1, 2, 3, 4, 5, 6, 10, 23 hours) at the doses of 100 mg and 200 mg of mirabegron [upper limit of two-sided 90% CI] were -0.80 to 3.06 [2.28-6.14] and 0.72 to 4.98 [3.77-8.03], respectively, and the value at any time point was < 10 ms. The difference from placebo in the mean changes in baseline-corrected QTcI interval at 3 hours after administration of moxifloxacin (t_{\max}) on Day 7 was 11.75 ms [14.80].

However, exploratory subgroup analysis by sex revealed that mirabegron did not prolong the QTcI interval in males, but the mean difference from placebo in the QTcI interval was affected by mirabegron in females; the maximum effect of 5.54 ms [8.74] was found at 5 hours post-dose in the mirabegron 100 mg group. The highest upper limit of two-sided 90% CI was 10.24 ms at 23 hours post-dose. In the mirabegron 200 mg group, the maximum effect was found at 10 hours post-dose, the mean difference from placebo in QTcI interval was 9.62 ms [13.17] and the highest upper limit of two-sided 90% CI was 13.90 ms at 3 hours post-dose. The upper limit of two-sided 90% CI exceeded 10 ms at 1 of 8 time points in the mirabegron 100 mg group and at 7 of 8 time points in the mirabegron 200 mg group. Categorical analysis of QTcI interval and changes from the baseline on Day 7 was performed. As a result, the subjects whose QTcI interval exceeded 450 ms were all female, and the percentage of the affected subjects following administration of the placebo, mirabegron 100 mg, mirabegron 200 mg, and moxifloxacin was 2.2% (1 of 46 subjects), 9.1% (4 of 44 subjects), 11.1% (5 of 45 subjects), and 13.3% (6 of 45 subjects), respectively. None of the subjects had QTcI interval > 480 ms. The percentage of the subjects with the QTcI interval change from the baseline > 30 ms in male and female subjects was 13.0% (3 of 23 subjects) and 8.7% (2 of 23 subjects), respectively, following administration of the placebo, 0%

(0 of 23 subjects) and 19.0% (4 of 21 subjects), respectively, following administration of mirabegron 100 mg, 4.3% (1 of 23 subjects) and 36.4% (8 of 22 subjects), respectively, following administration of mirabegron 200 mg, and 13.0% (3 of 23 subjects) and 27.3% (6 of 22 subjects), respectively, following administration of moxifloxacin, the change was greater in female subjects than in male subjects. None of the subjects had the QTcI interval change from the baseline >60 ms.

To further investigate the effect in females and to improve the precision and heart rate correction, which were used to detect differences in QTc interval changes, the analysis was performed again. The difference from placebo in the change from baseline in QTcI interval (which is QT interval corrected for heart rate using individual correction factor in male subjects) at the same time point (ddQTcI) was determined. As a result, the upper limit of two-sided 90% CI of ddQTcI at the doses of 100 and 200 mg of mirabegron did not exceed 10 ms at any time point. In female subjects, the upper limit of two-sided 90% CI of ddQTcI at the doses of 100 and 200 mg of mirabegron exceeded 10 ms at some time points (1 of 13 time points at the dose of 100 mg, 11 of 13 time points at the dose of 200 mg). The ddQTcI tended to be prolonged in female subjects.

In the pharmacokinetic-pharmacodynamic evaluation on the initial leading data, regression analysis was performed for the relationship between ddQTcI and plasma mirabegron concentration. As a result, no significant correlations were observed in the overall data or data from male subjects. In female subjects, a significant positive correlation was found between the plasma concentration and QTcI (slope = 0.02056, $P = 0.0491$). The heart rate increased with the plasma mirabegron concentration.

4.(ii).A.(7).2) Urodynamic study (Attached document 5.3.4.2-1, Study No. CL-060, Study period December 2006 to August 2008, Evaluation data)

Foreign male patients with lower urinary tract symptom (LUTS) and bladder outlet obstruction (BOO) received mirabegron once daily at the dose of 50 mg (64 patients) or 100 mg (58 patients), or placebo (63 patients) for 12 weeks. The lower limit of 95% CI of the difference in mean change from baseline in the maximum urinary flow rate (Q_{\max}) in the 50 mg and 100 mg groups was -0.63 and -0.43, respectively, falling within the predefined non-inferiority margin (-3 mL/s). The upper limit of 95% CI of the difference in mean change from baseline in the detrusor pressure at Q_{\max} ($P_{\det}Q_{\max}$) in the 50 mg and 100 mg groups was 2.09 and 6.96, respectively, which were smaller than the predefined non-inferiority margin of 15 cm H₂O. Based on the above, the applicant claims that once-daily administration of mirabegron at the dose of 50 or 100 mg for 12 weeks did not affect the $P_{\det}Q_{\max}$ or Q_{\max} in foreign male patients with LUTS and BOO.

4.(ii).B. Outline of the review by PMDA

4.(ii).B.(1) Nonlinear pharmacokinetics of mirabegron

PMDA considers that the nonlinear pharmacokinetics of mirabegron in non-clinical pharmacokinetic studies, which is more than dose-proportional increases of C_{\max} and AUC, was also noted in clinical pharmacology data from humans (e.g., Study CL-034, Study CL-066, and Study CL-031).

The applicant explained the reasons for the nonlinear pharmacokinetics of mirabegron in humans as follows:

In a study in foreign healthy adult subjects (Study CL-076), the mean total body clearance (CL_{tot}) following intravenous doses of 7.5, 15, and 30 mg of mirabegron was 58.2, 54.3, and 55.1 L/h, respectively, remaining consistent irrespective of the dose. In a study on gender-related differences and the elderly in foreign healthy adult subjects (Study CL-072), the ratio of each metabolite to unchanged mirabegron did not greatly differ among the doses. Based on the above, the applicant speculated that more than dose-proportional increases in C_{\max} and AUC of mirabegron were likely to be related to the absorption process, but not the metabolism process

subsequent to the systemic circulation. This would be mainly caused by the saturation of efflux capacity of mirabegron by small intestinal P-glycoprotein.

PMDA considers as follows:

The applicant's explanation that the non-linear pharmacokinetics of mirabegron is likely to be related to the absorption process is acceptable. Given that the long-term treatment safety study during the development stage of the proposed product demonstrated the safety of mirabegron at the doses up to 100 mg, and that the clinical pharmacokinetic studies investigated effects of endogenous and exogenous factors on pharmacokinetics of mirabegron at the doses of ≥ 100 mg [see "4.(iii).B.(5).1) Dosage"], the non-linear pharmacokinetics of mirabegron itself is unlikely to become clinically relevant problem in consideration that mirabegron is to be primarily used at 1 dose of 50 mg in clinical practice. However, concomitant use of mirabegron with drugs affecting the efflux mediated by P-glycoprotein in the small intestine may result in an elevation of blood mirabegron concentration, to which attention should be paid. Thus, it will be discussed in the "(7) Drug-drug interaction study" section.

4.(ii).B.(2) Appropriateness of methods for investigating pharmacokinetics of mirabegron

PMDA considers as follows:

For adequate investigation of pharmacokinetics of mirabegron, plasma concentration data covering a sufficiently long post-dose period based on $t_{1/2}$ of mirabegron should be collected. In consideration of long-term multiple administration of mirabegron, data on accumulation of mirabegron at steady state relative to that following the single dose serve as important information. In a Japanese phase I study in Japanese subjects (Study CL-034), plasma mirabegron concentrations were measured only until 72 hours post-dose, and the longest measurement period in clinical studies in Japanese subjects was 96 hours post-dose in Study CL-078. In these Japanese clinical studies, $t_{1/2}$ of mirabegron was approximately 35 hours, and in foreign Study CL-031, where the plasma mirabegron concentration was measured until 72 hours post-dose, the $t_{1/2}$ of mirabegron was also approximately 35 hours. On the other hand, in foreign Study CL-072, where the plasma mirabegron concentration was measured until 168 hours post-dose, the $t_{1/2}$ of mirabegron was approximately 65 hours. Therefore, the plasma concentration measurement periods in Japanese pharmacokinetic studies were not sufficiently long to obtain the comprehensive pharmacokinetic profile of mirabegron. The applicant compared the exposure at the NOAEL in a non-clinical repeated-dose toxicity study with that on Day 7 in Study CL-072 as the exposure at a clinical dose. However, as described above, in this study where $t_{1/2}$ of mirabegron was determined to be approximately 65 hours, the plasma mirabegron concentration may not have reached the steady state on Day 7.

Based on the above, it should be noted that pharmacokinetic parameters may have differed depending on plasma concentration measurement data from each clinical pharmacokinetic study due to the different measurement time points. Information about the pharmacokinetics in the package insert (draft) provided by the applicant includes $t_{1/2}$ and AUC_{inf} calculated or estimated from the data until 72 hours post-dose in a Japanese single dose clinical study. Therefore, the AUC_{inf} is unlikely to be adequately estimated. In addition, the draft package insert include no information on the pharmacokinetic parameters on Day 1 under a multiple dose regimen is not included, nor clear explanation on the pharmacokinetic characteristic of mirabegron in terms of its accumulation following multiple doses. The applicant should discuss the measures for providing sufficient information to clinical practice, at least presenting the AUC following the single dose calculated from the measured values until 72 hours post-dose as well as the pharmacokinetic parameters on Day 1 under the multiple dose regimen.

4.(ii).B.(3) Gender-related and age-related differences in pharmacokinetics of mirabegron

The applicant claimed that gender-related differences in the pharmacokinetics of mirabegron were mainly caused by differences of the body weight based on the following reasons: (i) in Study CL-078, after administration of mirabegron to Japanese healthy adult male and female subjects at the doses of 50 mg (1 mirabegron 50 mg tablet) and 100 mg (2 mirabegron 50 mg tablets) to investigate food effects on the pharmacokinetics, the plasma mirabegron concentrations in female subjects were higher than those in male subjects, but the difference was reduced by corrections according to the dose and body weight; and (ii) in Study CL-076 where a relationship between *in vitro* dissolution and absolute BA was investigated in foreign subjects, the absolute BA in female subjects was higher than that in male subjects.

Furthermore, the applicant claimed that age-related differences (effects in elderly) in the pharmacokinetics of mirabegron were small by presenting the following clinical data. In a study on gender-related difference and in elderly (Study CL-072) in foreign subjects, multiple doses of 25, 50, or 100 mg of mirabegron were administered to non-elderly healthy male and female subjects (19-45 years of age) or elderly male and female subjects (55-77 years of age). As a result, no difference was observed in C_{\max} or AUC_{τ} between elderly subjects aged ≥ 55 years and non-elderly subjects or even between elderly subjects aged ≥ 65 years and non-elderly subjects.

On the other hand, in a phase III study in Japanese OAB patients (Study CL-048), the plasma mirabegron concentrations at 18 to 30 hours post-dose were 1.325 times higher in patients aged ≥ 65 years than in those aged < 65 years. In consideration of the data from Study CL-048, PMDA asked the applicant to provide information that following administration of mirabegron to Japanese OAB patients, the plasma mirabegron concentrations were higher in elderly subjects than in non-elderly subjects. The applicant responded that specific information about the pharmacokinetics in the elderly and non-elderly subjects were to be provided.

PMDA considers as follows:

Action of the applicant to provide the information about pharmacokinetics of mirabegron in elderly subjects is appropriate. The applicant explained the gender-related differences in pharmacokinetics by comparing dose (mg/kg)-corrected plasma mirabegron concentrations between male and female subjects. However, the comparison does not clearly account for causes of the gender-related differences, since the absolute BA of mirabegron administered orally differs depending on the dose. It is necessary to appropriately provide the information that the blood concentrations in female subjects were higher than those in male subjects, taking into account that the gender-related differences in mirabegron concentrations have been indicated by the following backgrounds: (a) in Study CL-072, the AUC in female subjects is greater than that in male subjects; (b) in a drug-drug interaction study with ketoconazole, the blood concentrations in female subjects are higher than those in males subject; and (c) the thorough QT/QTc study suggests that a risk of QT prolonged is higher in female subjects than in male subjects, although factors other than the difference in drug concentrations may be involved.

4.(ii).B.(4) Ethnic differences in pharmacokinetics of mirabegron

The applicant explained ethnic differences in pharmacokinetics of mirabegron as follows:

Study CL-078, a Japanese study for food effects, and Study CL-041 (data 5.3.1.1-4), a foreign study for food effects (in the US), were conducted coincidentally at the same period in a comparable design. Using data from both studies, pharmacokinetics following single dose of mirabegron were compared between Japanese and foreign healthy subjects. As a result, C_{\max} and AUC_{\inf} of mirabegron administered in the fasted state tended to be higher in Japanese healthy subjects than in foreign subjects, but no difference was found in t_{\max} , and $t_{1/2}$ was slightly longer in foreign healthy subjects than in Japanese healthy subjects. The same results were observed in subjects receiving the drug after a meal. Comparison of subject demographics in both studies indicated a difference in mean body weight by approximately 20 kg, and there were major differences in the body weight. The differences were reduced in dose- and body-weight-corrected

C_{\max} and AUC_{inf} . Although variations among individuals were large, the ranges of these parameters shown in both studies were considered almost comparable.

PMDA considers as follows:

Comparisons of clinical pharmacokinetic data between Japanese and foreign subjects indicate that the plasma mirabegron concentrations were generally higher in Japanese subjects than in foreign subjects. Thus, the results of these studies cannot be deemed as the basis of the comparable pharmacokinetics between Japanese and foreign subjects, despite the applicant's claim that the differences were reduced in dose- and body-weight-corrected C_{\max} and AUC_{inf} . Therefore, the pharmacokinetics difference between Japanese and foreign subjects should be taken into account for evaluating the study data in foreign subjects.

4.(ii).B.(5) Thorough QT/QTc study data

PMDA considers as follows:

In the thorough QT/QTc study (Study CL-037), an analysis on the overall data did not indicate a risk of QT prolongation, but subgroup analysis by sex showed that the upper limit of two-sided 90% CI of $ddQTcI$ in female subjects in the mirabegron 100 mg and 200 mg groups exceeded 10 ms at some time points. Thus, a risk of QT prolonged cannot be ruled out for mirabegron. Plasma mirabegron concentrations were higher in Japanese subjects than in foreign subjects and had extremely large inter-individual variability, the exposures of mirabegron in the thorough QT/QTc study were within the range adequately predicted from some of the individual patients receiving mirabegron at the clinical dose. Thus, it is necessary to further investigate the risk of mirabegron-induced QT prolongation, also taking into account the incidence of adverse events related to QT prolongation in Japanese and foreign clinical studies. [see "4.(iii).B.(2).2) Cardiovascular risk"]

4.(ii).B.(6) Pharmacokinetics in patients with renal or hepatic impairment and appropriateness of dose adjustment in these patient populations

Taking into account that data from Study CL-038 and Study CL-039 showed that C_{\max} and AUC in patients with severe renal impairment and patients with moderate hepatic impairment were twice higher than those in the other subjects, at the submission, the applicant explained that the following dosage regimen is appropriate for patients with severe renal impairment and patients with moderate hepatic impairment; mirabegron should be initiated at 25 mg once daily and then the dose can be increased up to 50 mg once daily.

PMDA asked the applicant to explain whether or not it is appropriate to set a half of the usual dose as the dose used in patients with severe renal impairment and patients with moderate hepatic impairment based on the data from Study CL-038 and Study CL-039 where the dose of mirabegron was 100 mg, even though the pharmacokinetics of mirabegron were nonlinear in a dose range of 25 to 100 mg.

The applicant explained as follows:

Although the pharmacokinetics following oral dose of mirabegron was non-linear in a range of 25 to 100 mg, Study CL-076 for relationship between *in vitro* dissolution and BA demonstrate that CL_{tot} following intravenous administration remained almost constant irrespective of the dose, and effects of renal impairment and hepatic impairment on pharmacokinetics can occur after the absorption process, which caused the non-linear trends. Therefore, the effects of renal impairment and hepatic impairment on mirabegron distributed in the body are in the same level irrespective of the dose.

Taking into account that Study CL-045 demonstrated the efficacy of mirabegron 25 mg against OAB symptoms, and the incidence of adverse events at mirabegron 25 mg was lower than those at mirabegron 50 mg and 100 mg, it is appropriate to set the dosage regimen at mirabegron 25 mg for patients with moderate hepatic impairment (Child-Pugh score, 7-9) and patients with severe

renal impairment (eGFR, 15-29 mL/min/1.73 m²), who are considered to have a high risk from a safety point of view.

PMDA considers as follows:

It is appropriate to set a half of the usual dose as the starting dose for patients with severe renal impairment and patients with moderate hepatic impairment based on the data from Study CL-038 and Study CL-039 and to provide the caution statement that mirabegron should be used carefully in those patients. The applicant deleted from the package insert (draft) a description that the maximum dose for these patient populations should be 50 mg in association with the change of the clinical maximum dose to 50 mg [see “4.(iii).B.(5).1 Dosage”], and has provided the caution statement about dose increase on the package insert. However, the caution should not be recognized as a note under assumption that the dose will be increased, because it is important to use mirabegron with adequate cautions in these patient populations, in whom the efficacy and safety have been evaluated only in limited clinical studies although the safety of mirabegron was confirmed at the dose up to 100 mg in a long-term treatment study. The information about pharmacokinetics in patients with renal impairment only included the increase in AUC. It is desirable to include the 2-fold increase of C_{max} as well. Furthermore, the applicant should collect post-marketing information appropriately and take actions where necessary.

4.(ii).B.(7) Drug interactions

4.(ii).B.(7).1 Interactions mediated by CYP2D6 inhibitory effect of mirabegron

Concomitant use of mirabegron 160 mg (two 80 mg IR capsules) with metoprolol led to a 3.29-fold increase in AUC_{inf} of metoprolol, but the applicant did not include a caution against concomitant use of mirabegron with metoprolol in the “Precautions for concomitant use” section of the proposed package insert. PMDA asked the applicant to explain the reason and appropriateness for such an omission after discussing potential consequences of concomitant use of the to-be-marketed formulation of mirabegron with metoprolol.

The applicant responded as follows:

C_{max} and AUC_{24h} of 50 mg OCAS tablets were remarkably low, being 0.11 and 0.15 times those of 160 mg IR capsules, respectively (the table below). Accordingly, the increase in AUC of metoprolol in combination with mirabegron 50 mg would not exceed 3.29 times.

Table. Plasma pharmacokinetic parameters in healthy adult male subjects following multiple doses

Study No.	Formulation	Dose (mg)	C _{max} (ng/mL)	AUC _{24h} (ng·h/mL)
CL-005	IR capsules	160	297 ± 55	1700 ± 270
CL-031	OCAS tablets	50	32.8 ± 15.6	262 ± 104

mean ± SD, n = 12 for Study CL-005, n = 6 for Study CL-031

However, the applicant has decided to include the caution against concomitant use with metoprolol, as it cannot be ruled out that concomitant use of mirabegron with metoprolol may lead to an increase in AUC of metoprolol.

Since concomitant use of mirabegron with flecainide or propafenone, which were CYP2D6 substrates with the narrow therapeutic range, were prohibited in Study CL-048 and Study CL-051, PMDA asked the applicant to consider whether or not cautions should be provided about these drugs.

The applicant explained as follows:

Both flecainide and propafenone are antiarrhythmic agents, metabolized by CYP2D6. In Study CL-048 and Study CL-051, concomitant use of both drugs was therefore prohibited, taking the

safety in the subjects into account. For these drugs, adverse drug reactions such as QT prolongation and ventricular tachycardia (including Torsades de Pointes [TdP]) have been reported as with pimozone (package inserts of Tambocor Tablets 50 mg/Tambocor Tablets 100 mg and Pronon Tablets 100 mg/Pronon Tablets 150 mg), caution will be included in the “Precautions for concomitant use” section. However, the applicant has decided to provide a caution statement, separately from other CYP2D6 substrates, that concomitant use of these antiarrhythmic drugs may cause QT prolongation or ventricular tachycardia (including TdP) as with pimozone.

PMDA considers as follows:

In consideration that mirabegron also has a risk of QT prolongation [see “4.(ii).B.(5) Thorough QT/QTc study data”], mirabegron should not be administered in combination with antiarrhythmic CYP2D6 substrates, of which blood concentrations can be increased by concomitant use of mirabegron. The appropriateness of concomitant use with these drugs will be discussed at the Expert Discussion, taking into account not only their pharmacokinetic effects but also the facts that these antiarrhythmic agents have a narrow therapeutic range, and that administration of mirabegron to the patients taking such drugs itself raises concern, and a final decision on the above issue will be finalized.

4.(ii).B.(7).2) Interactions with drugs having CYP3A4 inhibitory effect or P-glycoprotein inhibitory effect

Since *in vitro* data have demonstrated that CYP3A4 and CYP2D6 are involved in the metabolism of mirabegron, CYP3A4 inhibitors are included in the “Precautions for concomitant use” section of the package insert. On the other hand, the applicant has explained that in Study ME-020, mirabegron was slowly metabolized in human liver microsome, resulting in production of the metabolites in small amounts. Also, some studies suggested that mirabegron is hydrolyzed by BuChE in human plasma (Attached document 5.3.2.3-4, 5.3.2.3-5). Therefore, PMDA asked the applicant to summarize the applicant’s view on the metabolic pathway of mirabegron in humans and to explain whether or not it is possible to draw the following conclusion: the increases in C_{max} and AUC of mirabegron in combination with ketoconazole as well as decreases in C_{max} and AUC of mirabegron in combination with rifampicin were consequences of the drug-drug interaction mediated by CYP3A4.

The applicant explained as follows:

Major metabolic enzymes of mirabegron in humans were inferred to include BuChE (M5, M16), glucuronidation enzyme (M11, M12, M13, M14), and CYP isoenzymes (M8, M15), of which CYP3A4 could be mainly involved in drug metabolism. In addition, a study for absolute BA (Study CL-033) has showed that CL_R following intravenous administration of mirabegron accounts for approximately 25% of CL_{tot} , indicating that renal excretion of unchanged mirabegron is one of the major elimination pathways. In the study for mass balance (Study CL-007), almost no peaks of the metabolites from the feces samples were observed, but that of unchanged mirabegron. Therefore, there were many metabolic and elimination pathways in mirabegron, and plasma mirabegron concentrations are unlikely to be remarkably increased by inhibition of CYP3A4. The increases in C_{max} and AUC of mirabegron in combination with ketoconazole, a potent CYP3A4 inhibitor, may be at least partially attributable to the drug interaction mediated by CYP3A4. However, ketoconazole has been known to inhibit P-glycoprotein and glucuronidation enzyme (U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry/Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling, Draft Guidance. [September 2006], *Clin Cancer Res.* 2005;11:6699-704), while mirabegron can serve as substrates of P-glycoprotein and glucuronidation enzyme. Therefore, the increases in C_{max} and AUC of mirabegron in combination with ketoconazole may be related to the drug interactions mediated by not only CYP3A4 but also P-glycoprotein and glucuronidation enzyme. On the other hand, following concomitant use of

mirabegron with rifampicin, a potent CYP3A4 inducer, the ratios of AUC_{last} of M8 and M15, metabolites potentially formed by CYP3A4, to that of unchanged mirabegron were 8.8 and 7.5 times that following administration of mirabegron alone (Study CL-070), indicating that the decreases in C_{max} and AUC of mirabegron in combination with rifampicin were related to the CYP3A4 induction. In Study CL-070, the ratios of AUC_{last} of M11, M13, and M14 (glucuronide conjugates of mirabegron) to that of unchanged mirabegron were also 1.7, 2.8, and 1.8 times, respectively, that following administration of mirabegron alone, and rifampicin is known to induce P-glycoprotein as well (*Clin Pharmacol Ther.* 2006;79:206-17). These findings suggests that the decreases in C_{max} and AUC of mirabegron in combination with rifampicin were attributable to the drug interactions mediated by not only CYP3A4 but also P-glycoprotein and glucuronidation enzyme.

PMDA highlighted the following findings: (i) *in vitro* data have suggested that mirabegron serves as a substrate of P-glycoprotein (Attached document 5.3.2.3-6); (ii) ketoconazole is a P-glycoprotein inhibitor and rifampicin is a P-glycoprotein inducer; (iii) the absolute BA of mirabegron is not high, and the plasma mirabegron concentration may be increased depending on the absorption profile; and (iv) non-clinical pharmacokinetic data show that excretion of mirabegron into bile cannot be excluded (Attached document 4.2.2.2-5). Based on these findings, and taking into account that the drug interaction of mirabegron with ketoconazole or rifampicin may be mediated by P-glycoprotein, PMDA asked the applicant to consider whether or not a caution should be provided for potential interactions with drugs having a similar mechanism to ketoconazole or rifampicin.

The applicant explained as follows:

The data on drug interaction of mirabegron with ketoconazole or rifampicin have indicated that inhibition against any of CYP3A4, P-glycoprotein, and glucuronidation enzyme may increase the plasma mirabegron concentration, and the effect of P-glycoprotein inhibition or induction on the plasma mirabegron concentration may be limited. As with ketoconazole, many of the CYP3A4 inhibitors also inhibit P-glycoprotein, and 8 potent CYP3A4 inhibitors listed in the “Precautions for concomitant use” section of the proposed package insert (draft) (itraconazole, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, clarithromycin, and telithromycin) include medications with P-glycoprotein inhibitory effect. Therefore, the additional inclusion of other CYP3A4 and P-glycoprotein inhibitors in the list is considered unnecessary at present. The applicant has decided to include a description in the PHARMACOKINETICS section of the package insert that mirabegron is a substrate of P-glycoprotein.

PMDA considers as follows:

It is appropriate to include CYP3A4 inhibitors and inducers in the “Precautions for concomitant use” section, based on the data on drug interaction of mirabegron with ketoconazole or rifampicin. As explained by the applicant, the effect of P-glycoprotein inhibitors on pharmacokinetics of mirabegron may be limited. However, it is appropriate to provide the information that not only CYP3A4 inhibition but also P-glycoprotein inhibition are involved in pharmacokinetic drug interactions of the drugs listed in the “Precautions for concomitant use” section, because the applicant has claimed that non-linear pharmacokinetics of mirabegron is attributable to P-glycoprotein, and non-clinical data have suggested that interactions of mirabegron with ketoconazole and rifampicin may be mediated by P-glycoprotein.

4.(ii).B.(8) Concentration-response relationship and PPK analysis performed by the applicant

Based on the PPK model established by analysis using the plasma concentration data obtained from Japanese phase I and phase II studies, the applicant calculated the mean plasma mirabegron concentration at steady state (C_{ss}), and described the relationship of C_{ss} with efficacy as follows: The relationship of C_{ss} of mirabegron with efficacy was evaluated in an exploratory manner, using

the weighted least squares method by plotting C_{ss} against primary and secondary endpoints, including change from baseline to the final visit in mean number of micturitions per 24 hours, change from baseline to the final visit in mean number of urgency episodes per 24 hours, change from baseline to the final visit in mean number of urinary incontinence episodes per 24 hours, and change from baseline to the final visit in mean volume voided per micturition. Results showed maximum effect for the change from baseline to the final visit in mean number of micturitions (primary endpoint) as well as change from baseline to the final visit in mean number of urgency episodes and change from baseline to the final visit in mean number of urinary incontinence episodes (secondary endpoints) around the plasma concentration in the 50 mg group.

The applicant used the PPK model to investigate the concentration-response relationship, but PMDA investigated the PPK analysis performed by the applicant.

The apparent CL of mirabegron is affected by covariates of both CL and F, but when covariates of CL and F in the final model were combined, many factors were detected as covariates of apparent CL. Therefore, PMDA asked the applicant to explain the view on whether or not the robustness of the model (stability of estimated parameters) is satisfactory.

The applicant responded as follows:

As a result of model validation by bootstrap, 181 of 250 data sets were determined to be successful in parameter estimation (regression success rate, 72.4%). The covariance matrix was not obtained in 31 data sets (12.4%) due to a rounding error. For others, the maximum likelihood estimation was terminated near the threshold in 28 data sets (11.2%), and 10 data sets (4.0%) were determined to have problems in calculation of maximum likelihood estimates according to the warning of excessive parameter values. However, no considerable differences were found in mean values of the fixed effect estimates for body height, total bilirubin, serum creatinine, sex, serum albumin, and age at any time of warning or termination, suggesting that estimates of these parameters were calculated with stability in general. For the data set with the maximum likelihood estimation terminated near the threshold, the termination near the threshold is speculated to be caused by the fact that the inter-individual variability of t_{lag} was 0.039, approaching 0. Hence, it is unlikely that the covariates selected for CL/F had affected the results. Therefore, the applicant claimed that the model had adequate robustness.

PMDA considers as follows:

The parameters obtained following regression failure lacked in reliability and it is difficult to explain the robustness of the model by presenting that these parameters were consequently comparable. The application of the PPK model established this time to the exploratory evaluation of concentration-response relationship is acceptable, but it is necessary to note that some demographic factors selected as covariates exhibited weak correlation between each other, and inclusion of many covariates may reduce the robustness of the model.

The appropriateness of the doses selected in the phase II studies will be continuously discussed in the Dosage and administration section [see “4.(iii).B.(5).1) Dosage”].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

The clinical study data submitted for this application are as shown in the table below. Data from the foreign phase II and phase III studies were submitted as reference data, while all the other data from clinical studies were submitted as evaluation data.

	Japanese/foreign	Study No.	
Phase I studies and pharmacokinetic studies	Phase I studies and pharmacokinetic studies in healthy adult subjects		
	Japanese	CL-034	Phase I single and multiple dose study
		CL-066	Dose proportionality study
		CL-064	Food-effect study
		CL-078	Food-effect study
	Foreign	CL-001	Single dose and food-effect study (IR capsules)
		CL-002	Multiple dose study (IR capsules)
		CL-007	Mass balance study
		CL-031	Multiple dose study on gender-related difference and in elderly
		CL-076	<i>In vitro-in vivo</i> correlation (IVIVC) study
		CL-030	OCAS formulation selection study
		CL-033	Absolute bioavailability study
		CL-041	Food-effect study
	Pharmacokinetic studies in patients		
	Japanese	CL-045	Phase II study (population pharmacokinetic analysis, concentration-response analysis, concentration-QTc correlation analysis)
		CL-048	Phase III study (trough concentration)
	Pharmacokinetic studies in special populations		
	Foreign	CL-072	Study on gender-related difference and in elderly
		CL-038	Pharmacokinetic study in patients with renal impairment
		CL-039	Pharmacokinetic study in patients with hepatic impairment
	Drug-drug interaction studies		
	Foreign	CL-036	Drug-drug interaction study (ketoconazole)
		CL-070	Drug-drug interaction study (rifampicin)
		CL-040	Drug-drug interaction study (warfarin)
		CL-005	Drug-drug interaction study (metoprolol)
		CL-058	Drug-drug interaction study (desipramine)
		CL-059	Drug-drug interaction study (digoxin)
		CL-006	Drug-drug interaction study (metformin)
		CL-068	Drug-drug interaction study (oral contraceptives)
	Pharmacodynamic studies		
	Foreign	CL-037	Thorough QT/QTc study
		CL-060	Urodynamics study
Studies in OAB patients	Japanese	CL-045	Phase II study
		CL-048	Phase III study
		CL-051	Phase III study (long-term treatment study)
	Foreign	CL-046	Phase II study
		CL-047	Phase III study
		CL-044	Phase II study
		CL-049	Phase III study (long-term treatment study)

4.(iii).A.(1) Japanese phase I studies

4.(iii).A.(1).1) Phase I single and multiple dose study (Attached document 5.3.3.1-1, Study No. CL-034, Study period ■ 20■ to ■ 20■, Evaluation data)

A single-blind study was conducted in Japanese healthy adult male subjects at a single center in Japan to investigate the safety and pharmacokinetics of mirabegron following single and multiple doses (target sample size, 64 subjects in total [Part 1, 40 subjects in the Step 1-5, 8 subjects per step (n = 6 on the active drug, n = 2 on placebo); Part 2, 24 subjects in the Step 6-7, 12 subjects per step

(n = 8 on the active drug, n = 4 on placebo)). In Part 1, a single dose of mirabegron (50, 100, 200, 300, 400 mg) or placebo was administered orally. In Part 2, a single dose of mirabegron (100, 200 mg) or placebo was administered orally, followed by a 2-day washout period, and then the study drug was administered for 7 days. A total of 64 subjects received the study drug.

In Part 1, adverse events occurred in 1 of 6 subjects (16.7%) in the 100 mg group, 3 of 6 subjects (50.0%) in the 300 mg group, and 4 of 6 subjects (66.7%) in the 400 mg group. Adverse events reported by ≥ 2 subjects included heart rate increased in 3 of 40 subjects (3 of 6 subjects in the 400 mg group) and blood amylase increased in 3 of 40 subjects (1 of 6 subjects in the 100 mg group, 2 of 6 subjects in the 300 mg group). In Part 2, adverse events occurred in 2 of 8 subjects (25.0%) in the placebo group, 2 of 8 subjects (25.0%) in the 100 mg group, and 1 of 8 subjects (12.5%) in the 200 mg group. Adverse event that was reported by ≥ 2 subjects was blood creatine phosphokinase increased (2 of 8 subjects in the placebo group, 1 of 8 subjects in the 100 mg group). There were no deaths, serious adverse events, or discontinuation due to adverse events in either Part 1 or Part 2.

4.(iii).A.(1).2) Dose proportionality study (Attached document 5.3.3.1-2, Study No. CL-066, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted in Japanese healthy adult male subjects at a single center in Japan (target sample size, 12 subjects) to investigate the pharmacokinetics and dose proportionality of mirabegron administered orally in a single dose. In the study, mirabegron was given to the same subject at 1 of 3 dose levels in each of 3 periods in a sequential manner. All subjects received single doses of 25 mg (Period 1), 50 mg (Period 2), and 100 mg (Period 3) sequentially, with a washout period of ≥ 12 days. A total of 12 subjects received the study drug. A total of 6 adverse events occurred in 4 of 12 subjects (33.3%), but there were no adverse events reported by >1 subject. There were no deaths, serious adverse events, or discontinuations due to adverse events.

4.(iii).A.(1).3) Food-effect study (Attached document 5.3.1.1-2, Study No. CL-064, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted in Japanese healthy adult male subjects at a single center in Japan (target sample size, 24 subjects) to investigate food effects on pharmacokinetics following administration of mirabegron 50 mg, a to-be-marketed formulation. The study was conducted as a 2-treatment, 2-period cross-over study, and 12 subjects were randomly assigned to each of 2 groups, of which one was to receive mirabegron in the fasted state and then in the fed state, and the other one was to receive it in the opposite sequence. Mirabegron 50 mg was to be administered orally in the fasted state or in the fed state, and a ≥ 12 -day washout period was included between the first dosing period and the second dosing period. The study enrolled a total of 24 subjects, who received the study drug. Regarding safety, 17 adverse events occurred in 10 of 24 subjects (41.7%), 13 adverse events occurred in 9 of 24 subjects (37.5%) following administration in the fasted state, and 4 events occurred in 3 of 24 subjects (12.5%) following administration in the fed state. Serious adverse events occurred in 1 subject who received mirabegron after a meal first, headache, pyrexia, and diarrhoea occurred following administration in the fasted state and did not resolve during the study period, but were confirmed to resolve at follow-up. These events were considered to be possibly related to the study drug. No deaths were observed, and discontinuation due to adverse events occurred in 1 subject who experienced serious adverse events (headache, pyrexia, and diarrhoea).

4.(iii).A.(1).4) Food-effect study (Attached document 5.3.1.1-3, Study No. CL-078, Study period July 2009 to September 2009, Evaluation data)

An open-label study was conducted in Japanese healthy adult subjects at 4 centers in Japan (target sample size, 72 subjects) to investigate food effects on pharmacokinetics following

administration of the mirabegron 50 mg, the to-be-marketed formulation, or 100 mg (2 × mirabegron 50 mg tablets). The study was conducted as a 3-period cross-over study; each subject received the study drug at the assigned dose under 3 different dosage regimens (administration in the fasted state, after a regular meal, and after a high-fat diet), the treatment in Period 2 and Period 3 was to be followed by a ≥ 12 -day washout period after the preceding treatment. A total of 72 subjects were included, 36 subjects were randomly assigned to each dose group (12 subjects were further assigned to each dosage regimen group) to receive the study drug. One subject each in the 50 mg group and 100 mg group voluntarily discontinued the study treatment after single dose in Period 2 and in Period 1, respectively.

Regarding safety, adverse events occurred in 20 of 36 subjects (55.6%) in the mirabegron 50 mg group and in 16 of 36 subjects (44.4%) in the mirabegron 100 mg group during the treatment period. There were no deaths, serious adverse events, or discontinuation due to adverse events. Adverse events reported by ≥ 2 subjects in any of the dosage regimens (in the fasted state, after a regular meal, after a high-fat diet) included diarrhoea, headache, somnolence, feeling hot, malaise, blood creatine phosphokinase increased, body temperature increased, and faeces hard.

4.(iii).A.(2) Japanese phase II study (Attached document 5.3.5.1-1, Study No. CL-045, Study period September 2007 to ■ 20■■, Evaluation data)

A randomized, double-blind, parallel-group study was conducted in OAB patients at 60 centers in Japan (target sample size; 180 subjects per group, 720 subjects in total) to investigate the efficacy (dose-response), safety, and pharmacokinetics following administration of mirabegron at the dose of 25 mg, 50 mg, 100 mg, or placebo.

The main inclusion criteria for provisional enrollment were outpatients who were aged ≥ 20 and ≤ 80 years and had OAB symptoms for at least 24 weeks before the start of the placebo run-in period. Then, the patients were to orally receive the placebo tablets once daily after breakfast during the 2-week placebo run-in period. For actual enrollment, patient diary records on 3 days during the placebo run-in period were checked. Based on the records, patients with a mean of ≥ 8 micturitions per 24 hours who met at least one of the following criteria were to enter the treatment period: (a) a mean of ≥ 1 urgency episodes per 24 hours and (b) a mean of ≥ 1 urge urinary incontinence episodes per 24 hours.

The study drugs were to be administered orally once daily after breakfast for 12 weeks during the treatment period in the following dosage regimens: 2 placebo tablets in the placebo group, 1 mirabegron 25 mg tablet + 1 placebo tablet in the mirabegron 25 mg group, 1 mirabegron 50 mg tablet + 1 placebo tablet in the mirabegron 50 mg group, and 2 mirabegron 50 mg tablets in the mirabegron 100 mg group.

Of 967 subjects provisionally enrolled, 125 subjects dropped out during the placebo run-in period (exclusion, 79 subjects; consent withdrawal, 24 subjects; adverse events, 9 subjects; and others), and 842 subjects were randomized (214 subjects in the placebo group, 211 subjects in the mirabegron 25 mg group, 208 subjects in the mirabegron 50 mg group, and 209 subjects in the mirabegron 100 mg group). A total of 838 subjects who had taken at least 1 dose of the double-blind study drug (212 subjects, 210 subjects, 208 subjects, and 208 subjects, respectively) were included in the safety analysis set, excluding 1 subject who was about to be enrolled in duplicate and 3 subjects who had not taken the study drug. A total of 835 subjects (211 subjects, 209 subjects, 208 subjects, and 207 subjects, respectively) who had taken at least 1 dose of the double-blind study drug and had undergone evaluation for at least 1 efficacy endpoint before and during the treatment period were included in the full analysis set (FAS) for efficacy variables. A total of 53 subjects (16 subjects, 11 subjects, 13 subjects, and 13 subjects, respectively) discontinued the study and the main reasons for discontinuation were adverse events (28 subjects), protocol deviation (12 subjects), and consent withdrawal (6 subjects).

Regarding efficacy, the mean number of micturitions at baseline and at the final visit (e.g., final evaluation) and the change in each group are as shown in the table below. For changes from baseline to the final visit in the mean number of micturitions per 24 hours (final visit – baseline) as the primary endpoint, significant differences were observed between all of the mirabegron groups and placebo group.

Table. Mean number of micturitions (FAS, Study CL-045)

	Placebo group (n = 211)	Mirabegron 25 mg group (n = 209)	Mirabegron 50 mg group (n = 208)	Mirabegron 100 mg group (n = 207)
Baseline	11.17 ± 2.526	11.47 ± 2.835	11.77 ± 2.606	11.20 ± 2.761
Final visit	9.99 ± 2.664	9.53 ± 2.550	9.65 ± 2.773	9.23 ± 2.622
Change (final visit – baseline)	-1.18 ± 2.155	-1.94 ± 2.158	-2.12 ± 2.383	-1.97 ± 1.970
<i>P</i> value* (compared with the placebo group)	—	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001

Measured values and changes are expressed as mean ± SD.

* Williams multiple comparison method (lower, one-sided significance level of 0.025)

Results of the major secondary endpoints including mean number of urgency episodes per 24 hours, mean number of urinary incontinence episodes per 24 hours, and mean number of urge urinary incontinence episodes per 24 hours are as shown in the table below.

Table. Results of the major efficacy secondary endpoints (FAS, Study CL-045)

Endpoint	Placebo group	25 mg group	50 mg group	100 mg group
Mean number of urgency episodes	n = 211	n = 208	n = 208	n = 207
Baseline	4.57 ± 3.160	4.68 ± 3.209	4.84 ± 3.255	4.53 ± 3.093
Final visit	2.74 ± 3.132	2.53 ± 3.013	2.60 ± 3.428	2.05 ± 2.585
Change (final visit – baseline)	-1.83 ± 2.965	-2.15 ± 2.731	-2.24 ± 3.120	-2.48 ± 2.605
<i>P</i> value*	—	— [§]	<i>P</i> = 0.084	<i>P</i> = 0.011
Mean number of urinary incontinence episodes	n = 140	n = 134	n = 144	n = 150
Baseline	1.68 ± 1.471	2.20 ± 2.499	2.00 ± 2.228	1.86 ± 1.666
Final visit	1.04 ± 1.856	0.91 ± 1.493	0.80 ± 1.546	0.59 ± 1.127
Change (final visit – baseline)	-0.64 ± 1.360	-1.29 ± 1.938	-1.20 ± 1.455	-1.28 ± 1.355
<i>P</i> value*	—	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001
Mean number of urge urinary incontinence episodes	n = 132	n = 128	n = 137	n = 142
Baseline	1.55 ± 1.376	1.97 ± 2.378	1.82 ± 2.098	1.77 ± 1.640
Final visit	0.86 ± 1.660	0.83 ± 1.435	0.72 ± 1.539	0.52 ± 1.017
Change (final visit – baseline)	-0.68 ± 1.358	-1.14 ± 1.809	-1.09 ± 1.345	-1.24 ± 1.278
<i>P</i> value*	—	<i>P</i> = 0.006	<i>P</i> = 0.008	<i>P</i> < 0.001

Mean ± SD

For the mean number of urinary incontinence episodes and mean number of urge urinary incontinence episodes, data in patients who had urinary incontinence at the baseline are shown.

* Williams multiple comparison (lower, one-sided significance level of 0.025), §: Excluded from the test

Regarding safety, the incidence of major adverse events during the treatment period are as shown in the table below. There were no deaths. During the treatment period, serious adverse events occurred in 4 of 212 subjects in the placebo group (subarachnoid haemorrhage, appendicitis, gastroenteritis, and anaemia [1 subject each]), 3 of 210 subjects in the mirabegron 25 mg group (cerebral infarction, clavicle fracture, and cerebral haemorrhage [1subject each]), 1 of 208 subjects in the mirabegron 50 mg group (spinal compression fracture in 1 subject), and 1 of 208 subjects in the mirabegron 100 mg group (Stevens-Johnson syndrome). Of those, a causal relationship to the study drug could not be ruled out for anaemia, cerebral haemorrhage, or Stevens-Johnson syndrome.

Table. Major adverse events during the treatment period (safety analysis population, Study CL-045)

	Placebo group (n = 212)	Mirabegron 25 mg group (n = 210)	Mirabegron 50 mg group (n = 208)	Mirabegron 100 mg group (n = 208)
Any adverse events reported	157 (74.1)	169 (80.5)	171 (82.2)	175 (84.1)
Nasopharyngitis	36 (17.0)	43 (20.5)	49 (23.6)	46 (22.1)
Alanine aminotransferase increased	4 (1.9)	7 (3.3)	8 (3.8)	12 (5.8)
Blood cholesterol increased	12 (5.7)	14 (6.7)	8 (3.8)	3 (1.4)
Blood creatine phosphokinase increased	29 (13.7)	25 (11.9)	21 (10.1)	31 (14.9)
Blood glucose increased	27 (12.7)	36 (17.1)	45 (21.6)	43 (20.7)
Gamma-glutamyltransferase increased	17 (8.0)	22 (10.5)	19 (9.1)	26 (12.5)
Protein urine present	14 (6.6)	22 (10.5)	21 (10.1)	28 (13.5)
White blood cell count decreased	5 (2.4)	6 (2.9)	8 (3.8)	11 (5.3)
Blood alkaline phosphatase increased	10 (4.7)	8 (3.8)	13 (6.3)	9 (4.3)
Urinary sediment abnormal	20 (9.4)	29 (13.8)	20 (9.6)	25 (12.0)

The value indicates the number of subjects (%).

Incidence of $\geq 5\%$ in any group

The incidence of adverse events during the treatment period leading to treatment discontinuation was 1.9% (4 of 212 subjects) in the placebo group, 2.4% (5 of 210 subjects) in the mirabegron 25 mg group, 3.4% (7 of 208 subjects) in the mirabegron 50 mg group, and 3.8% (8 of 208 subjects) in the mirabegron 100 mg group. Of these, adverse events reported by ≥ 2 subjects in any of the mirabegron groups included palpitations, malaise, hypertension (1 subject each in the mirabegron 50 mg group, 1 subject each in the mirabegron 100 mg group), and headache (2 subjects in the mirabegron 100 mg group).

4.(iii).A.(3) Japanese phase III study (Attached document 5.3.5.1-2, Study No. CL-048, Study period July 2009 to ■ 2010, Evaluation data)

A randomized, double-blind, parallel-group study was conducted in patients with OAB at 93 centers in Japan (target sample size; 330 subjects per group, 990 subjects in total) to investigate the efficacy, safety, and pharmacokinetics following administration of mirabegron 50 mg, tolterodine tartrate (tolterodine) 4 mg, and placebo.

The main inclusion criteria for provisional enrollment were patients who had OAB symptoms for ≥ 24 weeks before the start of the placebo run-in period. Then, all of the enrolled patients were to orally receive 1 placebo tablet for mirabegron and 1 placebo capsule for tolterodine once daily after breakfast for 2 weeks during the 2-week placebo run-in period. For actual enrollment, patient diary records on 3 days during the placebo run-in period were checked. Based on the records, patients with a mean of ≥ 8 micturitions per 24 hours who met at least one of the following criteria were to enter the treatment period: (a) a mean of ≥ 1 urgency episodes per 24 hours and (b) a mean of ≥ 1 urge urinary incontinence episodes per 24 hours.

The study drug was to be administered orally once daily after breakfast for 12 weeks during the treatment period in the following dosage regimens: 1 mirabegron 50 mg tablet + 1 placebo capsule for tolterodine in the mirabegron 50 mg group, 1 placebo tablet for mirabegron + 1 tolterodine 4 mg capsule in the tolterodine group, and 1 placebo tablet for mirabegron + 1 placebo capsule for tolterodine in the placebo group.

Of 1332 subjects provisionally enrolled, 193 subjects dropped out during the placebo run-in period (exclusion, 123 subjects; adverse events, 14 subjects; consent withdrawal, 34 subjects; protocol deviation, 8 subjects; other reasons, 14 subjects), and 1139 subjects were actually enrolled and randomized (381 subjects in the placebo group, 380 subjects in the mirabegron 50 mg group, and 378 subjects in the tolterodine 4 mg group). A total of 1133 subjects who had taken

at least 1 dose of the double-blind study drug (379 subjects, 379 subjects, and 375 subjects, respectively) were included in the safety analysis set. A total of 1105 subjects (368 subjects, 369 subjects, and 368 subjects, respectively) who had taken at least 1 dose of the double-blind study drug and had undergone evaluation for at least 1 efficacy endpoint before and after the treatment period were included in the FAS for efficacy variables. A total of 85 subjects (31 subjects, 31 subjects, and 23 subjects, respectively) discontinued the study during the treatment period and the main reasons for discontinuation were adverse events (37 subjects) and consent withdrawal (21 subjects).

Regarding efficacy, the mean number of micturitions at the baseline and at the final visit and the change in each group are as shown in the table below. For changes in the mean number of micturitions per 24 hours (final visit – baseline), the primary endpoint, significant differences were observed between the mirabegron 50 mg group and the placebo group.

Table. Mean number of micturitions (FAS, Study CL-048)

	Placebo group (n = 368)	Mirabegron 50 mg group (n = 369)	Tolterodine 4 mg group (n = 368)
Baseline	11.29 ± 2.748	11.15 ± 2.650	11.10 ± 2.567
Final visit	10.44 ± 2.777	9.48 ± 2.528	9.70 ± 2.629
Change (final visit – baseline)	–0.86 ± 2.354	–1.67 ± 2.212	–1.40 ± 2.176
<i>P</i> value*	—	<i>P</i> < 0.001	—

Mean ± SD

* Comparison between the mirabegron group and placebo group by two-sample t-test (two-sided significance level of 0.05)

Results of the major secondary endpoints including mean number of urgency episodes per 24 hours, mean number of urinary incontinence episodes per 24 hours, and mean number of urge urinary incontinence episodes per 24 hours are as shown in the table below.

Table. Results of the major efficacy secondary endpoints (FAS, Study CL-048)

Endpoint	Placebo group	Mirabegron 50 mg group	Tolterodine 4 mg group
Mean number of urgency episodes	n = 368	n = 369	n = 368
Baseline	4.42 ± 2.989	4.27 ± 2.848	4.13 ± 2.810
Final visit	3.05 ± 3.279	2.42 ± 2.835	2.48 ± 2.839
Change (final visit – baseline)	–1.37 ± 3.191	–1.85 ± 2.555	–1.66 ± 2.560
<i>P</i> value*	—	<i>P</i> = 0.025	—
Mean number of urinary incontinence episodes	n = 264	n = 266	n = 240
Baseline	1.91 ± 1.760	1.99 ± 2.054	1.89 ± 1.826
Final visit	1.25 ± 1.983	0.87 ± 1.671	0.92 ± 1.753
Change (final visit – baseline)	–0.66 ± 1.861	–1.12 ± 1.475	–0.97 ± 1.612
<i>P</i> value**	—	<i>P</i> = 0.003	—
Mean number of urge urinary incontinence episodes	n = 258	n = 254	n = 230
Baseline	1.67 ± 1.366	1.78 ± 1.752	1.71 ± 1.571
Final visit	1.06 ± 1.733	0.77 ± 1.485	0.77 ± 1.469
Change (final visit – baseline)	–0.60 ± 1.745	–1.01 ± 1.338	–0.95 ± 1.583
<i>P</i> value**	—	<i>P</i> = 0.008	—

Mean ± SD

For the mean number of urinary incontinence episodes and mean number of urge urinary incontinence episodes, data in patients who had urinary incontinence at the baseline are shown.

* Comparison with the placebo group by two-sample t-test (two-sided significance level of 0.05)

* Comparison between the mirabegron group and placebo group by Wilcoxon rank sum test (two-sided significance level of 0.05)

Regarding safety, major adverse events during the treatment period are as shown in the table below. There were no deaths. Four serious adverse events occurred in 4 subjects of the placebo group (facial bones fracture, uterine leiomyoma, loss of consciousness, meniscus lesion), 3 events in 3 subjects of the mirabegron 50 mg group (malignant anorectal neoplasm, patella fracture, pneumonia primary atypical), and 5 events in 4 subjects of the tolterodine group (femoral neck fracture, colitis, bacterial sepsis, pyelonephritis acute, Lemmel's syndrome). Of those, a causal relationship to the study drug could not be ruled out for loss of consciousness in the placebo group and colitis in the tolterodine group. The incidence of adverse events during the treatment period leading to treatment discontinuation was 2.1% (8 events in 8 subjects) in the placebo group, 3.2% (12 events in 12 subjects) in the mirabegron 50 mg group, and 3.2% (17 events in 12 subjects) in the tolterodine group.

Table. Major adverse events during the treatment period (safety analysis population, Study CL-048)

	Placebo group (n = 379)	Mirabegron 50 mg group (n = 379)	Tolterodine 4 mg group (n = 375)
Any adverse event reported	292 (77.0)	281 (74.1)	305 (81.3)
Dry mouth	11 (2.9)	10 (2.6)	53 (14.1)
Nasopharyngitis	58 (15.3)	50 (13.2)	41 (10.9)
Blood cholesterol increased	33 (8.7)	12 (3.2)	14 (3.7)
Blood creatine phosphokinase increased	53 (14.0)	49 (12.9)	57 (15.2)
Blood glucose increased	82 (21.6)	74 (19.5)	72 (19.2)
Gamma-glutamyltransferase increased	28 (7.4)	35 (9.2)	38 (10.1)
Glucose urine present	17 (4.5)	21 (5.5)	20 (5.3)
Protein urine present	26 (6.9)	23 (6.1)	15 (4.0)
Blood alkaline phosphatase increased	20 (5.3)	17 (4.5)	12 (3.2)
Urinary sediment abnormal	46 (12.1)	54 (14.2)	42 (11.2)

The value indicates the number of subjects (%).

Incidence of $\geq 5\%$ in any group

4.(iii).A.(4) Japanese long-term treatment study (Attached document 5.3.5.2-1, Study No. CL-051, Study period December 2008 to March 2010, Evaluation data)

An open-label, uncontrolled study was conducted in patients with OAB at 26 centers in Japan (target sample size, ≥ 150 subjects) to evaluate the safety and efficacy of long-term treatment with mirabegron 50 mg (The dose was allowed to be increased to 100 mg).

The main inclusion criteria for provisional enrollment were patients who had OAB symptoms for ≥ 24 weeks before the start of the placebo run-in period. For actual enrollment after the 1-week placebo run-in period, patients with a mean of ≥ 8 micturitions per 24 hours who met at least one of the following criteria (based on patient diary records on 3 days during the placebo run-in period) were to be transferred to the treatment period: (a) a mean of ≥ 1 urgency episodes per 24 hours and (b) a mean of ≥ 1 urge urinary incontinence episodes per 24 hours.

One mirabegron 50 mg tablet was to be administered once daily after breakfast for 52 weeks. The dose of mirabegron was allowed to be increased to 100 mg once daily (two 50 mg tablets) for the patients who were considered not to respond to the study drug sufficiently at the visit in Week 8 of the treatment and to have no safety issues. Once the dose was increased, the dose was not to be reduced until the end of study in principle unless adverse events occurred.

Of 231 subjects who provided the consent, 27 subjects dropped out during the placebo run-in period (exclusion, 14 subjects; consent withdrawal, 12 subjects; the other reasons, 1 subjects), and 204 patients were actually enrolled. Of these, 202 subjects who had taken at least 1 dose of

the study drug were included in the safety analysis set. Of 203 subjects treated with mirabegron, 145 subjects maintained the dose at 50 mg even after the visit in Week 8, 50 subjects continued the treatment at the increased dose of 100 mg, and 8 subjects discontinued the treatment before dose adjustment in Week 8 (adverse events, 5 subjects; insufficient effect, 1 subject; consent withdrawal, 2 subjects). Of 145 subjects who maintained the dose, 123 subjects completed the 52-week treatment, and 22 subjects discontinued the treatment (adverse events, 5 subjects; insufficient effect, 4 subjects; consent withdrawal, 3 subjects; protocol deviation, 1 subject). Of 50 subjects who continued the treatment at the increased dose, 40 subjects completed the 52-week treatment, 2 subjects completed the treatment at the reduced dose of 50 mg/day, and 8 subjects discontinued the treatment (adverse events, 5 subjects; consent withdrawal, 1 subject; and others).

Regarding safety, major adverse events are as shown in the table below. One death due to aortic dissection was reported during the study. While the investigator judged that the relationship of aortic dissection with mirabegron “can be ruled out,” the sponsor judged that the relationship to the study drug cannot be completely ruled out due to lack of the information at the time of death. Five serious adverse events other than death were reported in 4 subjects at the maintenance dose of 50 mg (appendicitis [2]; intestinal ischaemia, pyelonephritis acute, and ovarian neoplasm [1 each]) and 2 events in 2 subjects at the increased dose of 100 mg (colonic polyp and basal cell carcinoma [1 each]). The causal relationship to the study drug was ruled out for any event. A total of 15 subjects (7.4%) discontinued the treatment due to adverse events (10 subjects at the maintenance dose of 50 mg, 5 subjects at the increased dose of 100 mg).

Table. Major adverse events during the treatment period (safety analysis population, Study CL-051)

	All subjects (n = 202)	Subjects at the maintenance dose of 50 mg (n = 152)	Subjects at the increased dose of 100 mg (n = 50)
Any adverse events reported	189 (93.6)	139 (91.4)	50 (100)
Constipation	11 (5.4)	9 (5.9)	2 (4.0)
Cystitis	16 (7.9)	12 (7.9)	4 (8.0)
Nasopharyngitis	60 (29.7)	44 (28.9)	16 (32.0)
Alanine aminotransferase increased	10 (5.0)	9 (5.9)	1 (2.0)
Blood cholesterol increased	11 (5.4)	10 (6.6)	1 (2.0)
Blood creatine phosphokinase increased	41 (20.3)	31 (20.4)	10 (20.0)
Blood glucose increased	62 (30.7)	43 (28.3)	19 (38.0)
Blood potassium increased	4 (2.0)	1 (0.7)	3 (6.0)
Blood uric acid increased	7 (3.5)	4 (2.6)	3 (6.0)
Gamma-glutamyltransferase increased	22 (10.9)	17 (11.2)	5 (10.0)
Glucose urine present	13 (6.4)	7 (4.6)	6 (12.0)
White blood cell count decreased	15 (7.4)	13 (8.6)	2 (4.0)
Protein urine present	15 (7.4)	10 (6.6)	5 (10.0)
Blood alkaline phosphatase increased	9 (4.5)	6 (3.9)	3 (6.0)
Urinary sediment abnormal	47 (23.3)	30 (19.7)	17 (34.0)
Back pain	9 (4.5)	6 (3.9)	3 (6.0)
Insomnia	6 (3.0)	3 (2.0)	3 (6.0)

The value indicates the number of subjects (%).

Incidence of $\geq 5\%$ in any group

The efficacy endpoints were changes from baseline to final visit in each of the mean number of micturitions per 24 hours, mean number of urgency episodes per 24 hours, mean number of urinary incontinence episodes per 24 hours, and mean number of urge urinary incontinence episodes per 24 hours. The results are as shown in the table below.

Table. Results of major efficacy endpoints

	All subjects	Subjects at the maintenance dose of 50 mg	Subjects at the increased dose of 100 mg
Mean number of micturitions	n = 196	n = 146	n = 50
Baseline	11.15 ± 2.621	11.11 ± 2.600	11.27 ± 2.702
At the visit in Week 8	9.63 ± 2.362	9.23 ± 2.149	10.81 ± 2.574
Final visit	9.14 ± 2.142	8.95 ± 2.138	9.69 ± 2.077
Change (final visit – baseline)	–2.01 ± 2.599	–2.16 ± 2.673	–1.57 ± 2.341
Mean number of urgency episodes	n = 196	n = 146	n = 50
Baseline	4.95 ± 3.137	4.79 ± 2.993	5.43 ± 3.512
At the visit in Week 8	2.67 ± 2.738	2.13 ± 2.093	4.25 ± 3.669
Final visit	1.79 ± 2.498	1.48 ± 2.076	2.71 ± 3.309
Change (final visit – baseline)	–3.16 ± 2.935	–3.31 ± 2.948	–2.72 ± 2.884
Mean number of urinary incontinence episodes	n = 149	n = 104	n = 45
Baseline	2.08 ± 1.848	1.95 ± 1.632	2.40 ± 2.259
At the visit in Week 8	1.06 ± 1.623	0.77 ± 1.305	1.74 ± 2.050
Final visit	0.71 ± 1.600	0.65 ± 1.590	0.84 ± 1.631
Change (final visit – baseline)	–1.38 ± 1.656	–1.30 ± 1.400	–1.56 ± 2.143
Mean number of urge urinary incontinence episodes	n = 147	n = 103	n = 44
Baseline	1.88 ± 1.743	1.79 ± 1.581	2.11 ± 2.076
At the visit in Week 8	0.85 ± 1.491	0.55 ± 1.087	1.53 ± 2.016
Final visit	0.56 ± 1.426	0.46 ± 1.333	0.78 ± 1.617
Change (final visit – baseline)	–1.33 ± 1.563	–1.32 ± 1.401	–1.33 ± 1.909

Mean ± SD

For the mean number of urinary incontinence episodes and mean number of urge urinary incontinence episodes, data in subjects who had urinary incontinence at the baseline are shown.

4.(iii).A.(5) Foreign phase I studies and clinical pharmacology studies

4.(iii).A.(5).1 Absolute BA study (Attached document 5.3.1.1-1, Study No. CL-033, Study period ■ 20■■ to ■20■■, Evaluation data)

An open-label study was conducted in foreign healthy adult male subjects at a single center in the Netherlands (target sample size; 6 subjects per group, 12 subjects in total) to investigate the absolute BA of mirabegron. The study was conducted as a 2-treatment, 2-period cross-over study, 6 subjects were randomly assigned to either Group A or Group B (Group A, single oral dose of mirabegron 50 mg and single intravenous dose of mirabegron 15 mg [formulation for intravenous injection]; Group B, single oral dose of mirabegron 150 mg and single intravenous dose of mirabegron 50 mg [formulation for intravenous injection]), and of 6 subjects assigned to each group, 3 subjects were further randomly assigned to either oral dose first regimen or injection first regimen. Period 1 was followed by a ≥14-day washout period, and in Period 2, a formulation different from that in Period 1 was administered.

A total of 12 subjects were enrolled to receive the study drug. Regarding safety, no deaths, serious adverse events, or treatment discontinuation due to adverse events were reported. In this study, 13 adverse events occurred in 5 of 6 subjects (83.3%) following intravenous administration at the dose of 15 mg (abdominal discomfort/abdominal pain, and flatulence [3 each]; vomiting and diarrhoea [2 each]; and others), 9 events in 6 of 6 subjects (100%) following intravenous administration at the dose of 50 mg (fatigue/asthenia [2] and others), 9 events in 4 of 6 subjects (66.7%) following oral administration at the dose of 50 mg (flatulence [2] and others), and 7 events in 5 of 6 subjects (83.3%) following oral administration at the dose of 150 mg (headache [3] and others).

4.(iii).A.(5).2 Food-effect study (Attached document 5.3.1.1-4, Study No. CL-041, Study period May 2009 to July 2009, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in the US (target sample size, 36 subjects per each dose group [18 each of male and female subjects], 72 subjects in total) to investigate food effects on the pharmacokinetics following single oral dose of mirabegron 50 mg (to-be-marketed formulation) or 100 mg (100 mg tablets). The food effects following administration in the fasted state, after a high-fat diet, and after a low-fat diet were investigated in a 6-treatment, 3-period cross-over manner (a washout period of ≥ 10 days). Subjects were randomized to 6 study treatment sequences for each of the 50 mg group and 100 mg group. Mirabegron (50, 100 mg) was to be administered orally at 30 minutes after the start of breakfast. A total of 76 subjects were randomized (38 subjects in the 50 mg group, 38 subjects in the 100 mg group) to receive the study drug. Of these, 3 subjects in the 50 mg group (consent withdrawal, 1 subject; protocol violation, 1 subject; other reasons, 1 subject) and 9 in the 100 mg group (protocol violation and consent withdrawal, 3 subjects each; adverse events, 2 subjects; lost to follow-up, 1 subject) discontinued the study treatment.

Adverse events occurred in 21 of 38 subjects (55.3%) in the 50 mg group and in 23 of 38 subjects (60.5%) in the 100 mg group. Commonly reported adverse events during the study period (reported by ≥ 2 subjects overall) included gastrointestinal disorder (nausea) and nervous system disorder (headache). Hypersensitivity reactions such as papule and rash pruritic were reported by 2 subjects in the 100 mg group. There were no deaths or serious adverse events. In addition, 2 subjects (both in the 100 mg group) discontinued the study treatment due to atrioventricular block second degree or hypertension.

4.(iii).A.(5).3) OCAS formulation selection study (Attached document 5.3.1.2-1, Study No. CL-030, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects in a single center in the Netherlands (target sample size; 12 subjects per group, 36 subjects in total) to compare the pharmacokinetics of mirabegron following administration of 3 types of oral-controlled absorption system tablets (OCAS formulations) in the fasted state and with that following administration of an immediate-release (IR) formulation in the fasted state. The study was conducted as a 3-treatment, 3-period cross-over study consisting of 3 groups by OCAS formulation (Group A, OCAS-Fast [OCAS-F]; Group B, OCAS-Slow [OCAS-S]; Group C, OCAS-Medium [OCAS-M]).

The study drugs were to be administered for each treatment period in each group according to the following dosage regimens: (i) each OCAS formulation (200 mg once daily) in the fed state for 8 days, (ii) each OCAS formulation (200 mg once daily) in the fasted state for 8 days, and (iii) IR capsule (100 mg twice daily) in the fasted state for 8 days. The treatment sequences were randomized. A washout period of ≥ 7 days was included between the treatment periods. A total of 36 subjects were randomized (12 subjects in Group A, 12 subjects in Group B, and 12 subjects in Group C) to receive study drug. The study treatment was discontinued in 1 subject each in Group C and Group A due to protocol deviation and adverse events, respectively.

Adverse events occurred in 12 of 12 subjects (100%) in Group A, in 12 of 12 subjects (100%) in Group B, and in 9 of 12 subjects (75.0%) in Group C. Commonly reported adverse events included headache, keratoconjunctivitis sicca, and palpitations. There were no deaths, and a serious adverse event occurred in 1 subject in Group A (neuropathy peripheral), of which a causal relationship to the study drug was ruled out.

4.(iii).A.(5).4) *In vitro-in vivo* correlation (IVIVC) study (Attached document 5.3.1.3-1, Study No. CL-076, Study period ■ 2009 to July 2009, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in the US as a 6-treatment, 5-period cross-over study (target sample size; 30 subjects per dose group, 90 subjects in total) to investigate the pharmacokinetics of mirabegron following oral administration of OCAS formulations with different release rates and intravenous administration of the

formulation for intravenous injection. The study consisted of 3 dose groups (dose of the formulation for intravenous injection [IV]/OCAS tablets [PO]; 7.5 mg/25 mg, 15 mg/50 mg, and 30 mg/100 mg). In each dose group, mirabegron was to be administered intravenously over 120 minutes in the first period, 1 of 3 types of mirabegron OCAS tablets was to be administered orally as a single dose in 1 period among the second to fourth periods (randomized to 1 of 6 treatment sequences), and then mirabegron OCAS tablets with the target release rate in a different lot were to be administered in the fifth period. Each treatment period lasted 5 days and a washout period of ≥ 10 days was included between the treatment periods.

A total of 91 subjects were randomized (30 subjects in the 7.5 mg IV/25 mg PO group, 30 subjects in the 15 mg IV/50 mg PO group, 31 subjects in the 30 mg IV/100 mg PO group) to receive study drug. Of these, 4 subjects in the 7.5 mg IV/25 mg PO group (protocol violation, 3 subjects; consent withdrawal, 1 subject), 5 subjects in the 15 mg IV/50 mg PO group (protocol violation, 2 subjects; consent withdrawal, 2 subjects; adverse events, 1 subject), and 7 subjects in the 30 mg IV/100 mg PO group (protocol violation, 1 subject; consent withdrawal, 2 subjects; adverse events, 3 subjects; discontinuation of intravenous infusion due to a request from the sponsor [the investigator decided the treatment discontinuation due to prolonged QTcB in electrocardiography at the baseline], 1 subject) discontinued the study treatment.

Adverse events occurred in 20 of 30 subjects (66.7%) in the 7.5 mg IV/25 mg PO group, in 22 of 30 subjects (73.7%) in the 15 mg IV/50 mg PO group, and in 25 of 31 subjects (80.6%) in the 30 mg IV/100 mg PO group. The most commonly reported adverse event was headache, and the incidence was 30.0% (9 of 30 subjects) in the 7.5 mg IV/25 mg PO group, 43.3% (13 of 30 subjects) in the 15 mg IV/50 mg PO group, and 22.6% (7 of 31 subjects) in the 30 mg IV/100 mg PO group. The applicant discussed that no notable differences were observed in adverse events among the dose groups or among the formulations. There were no deaths, and serious adverse events included pregnancy and abortion spontaneous in 1 subject in the 15 mg IV/50 mg PO group and leukocytoclastic vasculitis in 1 subject in the 30 mg IV/100 mg PO group. The pregnancy and abortion spontaneous in 1 subject were considered to be unrelated to the study drug, while the leukocytoclastic vasculitis in 1 subject was considered to be probably related. Adverse events leading to treatment discontinuation occurred in 3 subjects in the 30 mg IV/100 mg PO group (rash maculo-papular, leukocytoclastic vasculitis, and Wolff-Parkinson-White syndrome [1 subject each]) and in 1 subject in the 15 mg IV/50 mg PO group (bacterial urethral infection).

4.(iii).A.(5).5) Single dose and food-effect study (IR capsules) (Attached document 5.3.3.1-3, Study No. CL-001, Study period ■ 20■■■ to ■ 20■■■, Evaluation data)

A clinical study was conducted in foreign healthy adult male subjects at a single center in the UK (target sample size; 88 subjects for Part 1, 12 subjects for Part 2) to investigate the safety, pharmacokinetics, and food effects following single dose of mirabegron IR capsules. Part 1 consisted of 10 mirabegron dose groups (0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, 340 mg), and 8 subjects were randomly assigned to each of the dose groups (6 subjects on the active drug, 2 subjects on placebo) except for the 100 mg group, to which a total of 16 subjects were assigned (12 subjects for the active drug, 4 subjects for the placebo) as a single dose was to be repeated twice. In each group, the single dose was to be administered orally in the fasted state. Part 2 was carried out as a 3-treatment, 3-period cross-over study; a single dose of mirabegron (160 mg) was to be administered after a meal, in the fasted state, and before a meal, and a 7-day washout period was included between the treatment periods. The study drug was administered to 85 subjects in Part 1 and to 12 subjects in Part 2.

Regarding safety, 64 adverse events occurred in 36 of 85 subjects (42.4%) (48 events in 27 of 65 subjects treated with the active drug [41.5%], 16 events in 9 of 20 subjects treated with the placebo [45.0%]) in Part 1. Adverse events reported by ≥ 3 subjects in total included dizziness postural (21 subjects), headache (17 subjects), upper respiratory tract infection (4 subjects), and

dizziness (3 subjects), and the incidence was clearly increased in the 340 mg group compared with the other dose groups including the placebo group. In Part 2, 12 adverse events occurred in 8 of 12 subjects (66.7%), and adverse events reported by ≥ 2 subjects included headache (4 subjects), shoulder pain (3 subjects), and dizziness postural (2 subjects). In either Part 1 or Part 2, no deaths, serious adverse events, or adverse events leading to treatment discontinuation were observed.

4.(iii).A.(5).6) Multiple dose study (IR capsules) (Attached document 5.3.3.1-4, Study No. CL-002, Study period ■ 20■■ to ■ 20■■, Evaluation data)

A clinical study was conducted in foreign healthy adult male subjects at a single center in the UK (target sample size; 40 subject, 8 subjects per dose group [6 subjects for the active drug, 2 subjects for the placebo]) to investigate the safety and pharmacokinetics following multiple administrations of mirabegron IR capsules. A single dose of mirabegron (IR capsules; 40, 80, 160, 240 mg) or placebo was administered to subjects in the active drug groups and the placebo group on Day 1, and then administered once daily in the fasted state from Day 3 to Day 9. To evaluate food effects on the pharmacokinetics, a 240 mg group in which the mirabegron was administered once daily in the fed state was added. A total of 40 subjects received the study drug, and 2 subjects who met the discontinuation criteria on heart rate (1 subjects each of the 240 mg group and 240 mg fed treatment group) discontinued the study treatment.

Regarding safety, adverse events occurred in 29 of 40 subjects (72.5%) (2 of 6 subjects in the 40 mg group, 6 of 6 subjects in the 80 mg group, 6 of 6 subjects in the 160 mg group, 6 of 6 subjects in the 240 mg group, 5 of 6 subjects in the 240 mg fed treatment group, 4 of 8 subjects in the placebo group [in the fasted state], 0 of 2 subjects in the placebo group [in the fed state]). Adverse events reported by ≥ 3 subjects in any active drug group included headache, palpitations, orthostatic hypotension, nausea, and amblyopia. There were no deaths, and a serious adverse event occurred in 1 subject in the 80 mg fasted treatment group (renal pain).

4.(iii).A.(5).7) Mass balance study (Attached document 5.3.3.1-5, Study No. CL-007, Study period ■ 20■■ to ■ 20■■, Evaluation data)

An open-label study was conducted in foreign healthy adult male subjects at a single center in the Netherlands (target sample size, 4 subjects) to investigate the metabolism/excretion pathways of mirabegron and the related data following a single oral dose of ^{14}C -labeled mirabegron. In the study, a single dose of 160 mg of ^{14}C -labeled mirabegron was administered in the fasted state, and 4 subjects received the study drug. Adverse events occurred in 3 of 4 subjects (75.0%) (somnolence [2], etc.). No deaths or serious adverse events were reported.

4.(iii).A.(5).8) Multiple dose study on gender-related difference and in elderly (Attached document 5.3.3.1-7, Study No. CL-031, Study period ■ 20■■ to ■ 20■■, Evaluation data)

A clinical study was conducted in foreign healthy non-elderly (18-55 years of age) and healthy elderly (65-80 years of age) subjects at 2 centers in the Netherlands (target sample size; 16 subjects per dose group, 8 each of male and female subjects [6 subjects for the active drug, 2 subjects for the placebo], 96 subject in total) to investigate the pharmacokinetics, safety, and tolerability following multiple administrations of mirabegron. The healthy non-elderly subjects were assigned to any of the 50, 100, 200, and 300 mg groups, and healthy elderly subjects were assigned to either 50 or 200 mg group. The subjects were to be hospitalized for the study. The study drug was to be administered in a single dose on Day 2 followed by multiple administration of the study drug once daily for 10 days from Day 5 to Day 14.

A total of 96 subjects were randomized to receive the study drug. A total of 430 adverse events occurred in 77 of 96 subjects (80.2%) (355 events in 57 of 72 subjects of the active drug group [79.2%], 75 events in 20 of 24 subjects of the placebo group [83.3%]). Commonly reported

adverse events in the active drug group or placebo group included headache (34.7% in the active drug group and 20.8% in the placebo group), dizziness (20.8% and 8.3%, respectively), palpitations (15.3% and 8.3%, respectively), abdominal pain (12.5% and 4.2%, respectively), and diarrhoea (8.3% and 16.7%, respectively). The applicant explained that the number of adverse drug reactions was increased with increasing dose, and the incidence was higher in non-elderly subjects than in elderly subjects. No deaths, serious adverse events, or treatment discontinuation due to adverse events were reported.

4.(iii).A.(5).9) Study on gender-related difference and in elderly (Attached document 5.3.3.3-1, Study No. CL-072, Study period 2009 to November 2009, Evaluation data)

An open-label study was conducted at a single center in France (target sample size; 36 non-elderly subjects, 36 elderly subjects [18 each of male and female subjects], 72 subjects in total) in healthy non-elderly (aged ≥ 18 years and ≤ 45 years) and healthy elderly (aged ≥ 55 years, subjects aged > 70 years should account for $\geq 25\%$) subjects to investigate the pharmacokinetics of mirabegron and its metabolites. The study consisted of 2 periods: Periods 1 and 2 (including a washout period of ≥ 14 days); subjects were randomized to 1 of 6 different combinations of the dose and the sequence was used in Periods 1 and 2 (25 mg \rightarrow 50 mg, 50 mg \rightarrow 25 mg, 25 mg \rightarrow 100 mg, 100 mg \rightarrow 25 mg, 50 mg \rightarrow 100 mg, 100 mg \rightarrow 50 mg) (in consideration of age and sex). In each period, mirabegron at the specified dose was to be administered orally twice daily (after breakfast and dinner) on Day 1 and then once daily (after breakfast) from Day 2 to Day 7.

A total of 75 subjects received the study drug, and of these, 8 subjects discontinued the study (consent withdrawal, 1 subject; serious adverse events, 1 subject; ineligible case at the screening in the second period, 6 subjects). A total of 42 adverse events occurred in 24 of 75 subjects (32.0%). Adverse events reported by ≥ 3 subjects overall included hot flush (in 5 of 75 subjects), headache (in 4 of 75 subjects), nausea and dry mouth (both in 3 of 75 subjects). There were no deaths. A serious adverse event of epilepsy occurred in 1 subject (at the dose of 100 mg), who discontinued the study due to the adverse event. The event was judged to be “possibly related” to the study drug.

4.(iii).A.(5).10) Pharmacokinetic study in patients with renal impairment (Attached document 5.3.3.3-2, Study No. CL-038, Study period September 2008 to September 2009, Evaluation data)

An open-label study was conducted in subjects with mild, moderate, and severe renal impairment who had not received renal dialysis and subjects with normal renal function at 2 centers in the US (target sample size, 32 subject) to investigate effects of renal impairment on the pharmacokinetics of mirabegron. According to the estimated glomerular filtration rate (eGFR), renal function at the baseline in the subjects was classified into 4 grades: normal, mild renal impairment (eGFR, 60-89 mL/min/1.73 m²), moderate renal impairment (eGFR, 30-59 mL/min/1.73 m²), and severe renal impairment (eGFR, 15-29 mL/min/1.73 m²), and 8 subjects were to be assigned to the corresponding renal function group. To measure clearance of iothalamate, iothalamate meglumine was to be administered 1 day before administration of mirabegron, and a single dose of mirabegron 100 mg tablet was to be administered orally in the following morning (Day 1). A total of 33 subjects received the study drug, and 1 subject in the severe renal impairment group discontinued the study after administration of the study drug due to difficulty of intravenous administration. Regarding safety, adverse events occurred in 0 of 8 subjects (0%) in the normal group, in 2 of 8 subjects (25.0%) in the mild renal impairment group, in 2 of 8 subjects (25.0%) in the moderate renal impairment group, and in 1 of 9 subjects (11.1%) in the severe renal impairment group. There were no adverse events reported by ≥ 2 subjects. No deaths or serious adverse events were reported.

4.(iii).A.(5).11) Pharmacokinetic study in patients with hepatic impairment (Attached

document 5.3.3.3-3, Study No. CL-039, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted at a single center in Slovakia (target sample size, 32 subjects) to compare pharmacokinetics following a single dose of 100 mg of mirabegron between patients with mild and moderate hepatic impairment and subjects with normal hepatic function. Patients with hepatic impairment were classified as those with mild hepatic impairment and those with moderate hepatic impairment according to the Child-Pugh score, and 8 patients each in the same severity were to be included in 1 of the 2 groups (16 patients in total). In addition, 8 subjects with normal hepatic function who had comparable characteristics in terms of age, sex, and BMI to patients in each group were to be enrolled (16 subjects in total). On Day 1, a single dose of mirabegron 100 mg was administered orally.

A total of 32 subjects received the study drug. No adverse events were reported in subjects with normal hepatic function or mild hepatic impairment, and diarrhoea occurred in 1 subject with moderate hepatic impairment. No deaths or serious adverse events were reported.

4.(iii).A.(5).12) Drug-drug interaction study (ketoconazole) (Attached document 5.3.3.4-1, Study No. CL-036, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in the US (target sample size, 24 subjects [12 each of male and female subjects]) to investigate the pharmacokinetic interaction between a single dose of mirabegron and multiple doses of ketoconazole. In Period 1, mirabegron (100 mg) was administered orally in a single dose in the fasted state on Day 1. In Period 2, mirabegron (100 mg) was administered orally in a single dose in the fasted state on Day 4, and ketoconazole (400 mg) was administered orally once daily in the fasted state from Day 1 to Day 9.

A total of 24 subjects received the study drug. Of these, 1 subject was not enrolled for Period 2 because the criteria for vital signs were not met due to fluctuation of the pulse rate after the end of Period 1. Commonly reported adverse events throughout the study included headache (15 of 24 subjects, 62.5%), nausea (5 of 24 subjects, 20.8%), rhinorrhoea (5 of 24 subjects, 20.8%), and fatigue (4 of 24 subjects, 16.7%). No deaths, serious adverse events, or treatment discontinuation due to adverse events were observed.

4.(iii).A.(5).13) Drug-drug interaction study (rifampicin) (Attached document 5.3.3.4-2, Study No. CL-070, Study period October 2008 to ■ 2008, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in the US (target sample size, 24 subjects [≥ 8 each of male and female subjects]) to investigate effects of multiple doses of rifampicin on the pharmacokinetics of a single dose of mirabegron. On Day 1, a single dose of 100 mg of mirabegron (one 100 mg tablet) was administered orally followed by a 3-day washout period, and then multiple dose of 600 mg of rifampicin (two 300 mg capsules) was administered orally from Day 5 to Day 15. On Day 12, mirabegron was also administered at a dose of 100 mg.

A total of 24 subjects received the study drug, and all of them experienced adverse events (2 of 24 subjects following administration of mirabegron alone, 24 of 24 subjects following administration of rifampicin alone, 4 of 24 subjects following concomitant administration of mirabegron + rifampicin). Major adverse events included chromaturia (23 subjects following administration of rifampicin alone, 1 subjects following concomitant administration of mirabegron + rifampicin), faeces discoloured (10 subjects following administration of rifampicin alone, 1 subjects following concomitant administration of mirabegron + rifampicin), and headache (2 subjects following administration of mirabegron alone, 1 subjects following concomitant administration of mirabegron + rifampicin). No deaths, serious adverse events, or

treatment discontinuation due to adverse events were reported.

4.(iii).A.(5).14) Drug interaction study (warfarin) (Attached document 5.3.3.4-3, Study No. CL-040, Study period ■ 2008 to ■ 20■■, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in France (target sample size, 24 subjects [12 each of male and female subjects]) to investigate effects of mirabegron on the pharmacokinetics of warfarin. On Day 1, a single dose of 25 mg of warfarin (five 5 mg tablets) was to be administered orally in the fasted state, followed by a 14-day washout period, and then multiple dose of 100 mg of mirabegron (one 100 mg tablets) was to be administered orally once daily in the fasted state for 16 days, from Day 15 to Day 30. On Day 23, warfarin was to be also administered at the dose of 25 mg.

A total of 24 subjects received the study drug. Regarding safety, adverse events occurred in 2 of 24 subjects following administration of warfarin alone, in 3 of 24 subjects following administration of mirabegron alone and in 3 of 24 subjects following administration of mirabegron + warfarin. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

4.(iii).A.(5).15) Drug interaction study (metoprolol) (Attached document 5.3.3.4-4, Study No. CL-005, Study period ■ 20■■ to ■ 20■■, Evaluation data)

An open-label study was conducted in foreign healthy adult male subjects who were determined to be PM or EM according to the genotype and phenotype of CYP2D6 at a single center in the Netherlands (target sample size; 8 subjects each of PM and EM in Part 1; 12 subjects of EM in Part 2) to investigate the pharmacokinetics following administration of mirabegron (IR capsules) alone and following concomitant use of mirabegron with metoprolol. In Part 1, a single dose of 160 mg of mirabegron (two 80 mg IR capsules) was to be administered to PM and EM subjects in the fasted state. In Part 2, 100 mg of metoprolol tartrate (one 100 mg tablet) was to be administered once daily to EM subjects in the fasted state on Day 1, followed by a 1-day washout period, and then mirabegron 160 mg (two 80 mg IR capsules) was to be administered once daily in the fasted state from Day 3 to Day 7. On Day 7, metoprolol tartrate was to be administered concomitantly with mirabegron at the dose of 100 mg.

Of 121 subjects who had undergone genetic test, 78 subjects were determined to be PM or EM. Of these, 8 each of PM and EM subjects included in Part 1 and 12 EM subjects included in Part 2 to receive the study drug. Regarding safety, adverse events occurred in 10 of 16 subjects (62.5%) in Part 1 (4 of 8 PM subjects, 6 of 8 EM subjects). Adverse events reported by ≥ 2 subjects were palpitations (3 subjects) and dizziness postural (2 subjects). In Part 2, adverse events reported by ≥ 2 subjects included ALT increased, headache (4 subjects each), and palpitations (3 subjects). In Part 1 and Part 2, no deaths or serious adverse events were observed.

4.(iii).A.(5).16) Drug interaction study (desipramine) (Attached document 5.3.3.4-5, Study No. CL-058, Study period ■ 20■■ to ■ 20■■, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in France (target sample size, 28 subjects [14 each of male and female subjects]) to investigate effects of multiple doses of mirabegron on the pharmacokinetics of desipramine. In Period 1, a single dose of 50 mg of desipramine (two 25 mg tablets) was administered orally in the fasted state on Day 1, and multiple dose of 100 mg of mirabegron (one 100 mg tablet) was administered orally daily in the fasted state from Day 5 to Day 23. On Day 18, desipramine was administered orally at the single dose of 50 mg. After a 13-day washout period (Day 24-36), desipramine (50 mg) was administered orally in a single dose on Day 38 in Period 2. A total of 28 subjects received the study drug, and 17 adverse events occurred in 9 of 28 subjects (32.1%). Adverse events reported by ≥ 2 subjects during each treatment period were abdominal pain in 2 of 28 subjects and faeces hard in 3 of 28 subjects in the mirabegron alone group as well as dysmenorrhoea in 2 of 28

subjects in the mirabegron + desipramine group. One subject discontinued the study after receiving drugs prescribed for sinusitis in the washout period, which met the exclusion criteria, but the event was considered to be unrelated to the study drug. No deaths or serious adverse events were reported.

4.(iii).A.(5).17) Drug-drug interaction study (digoxin) (Attached document 5.3.3.4-6, Study No. CL-059, Study period ■ 20■ to ■ 20■, Evaluation data)

An open-label study was conducted in foreign healthy adult subjects at a single center in France (target sample size, 24 subjects [12 each of male and female subjects]) to investigate effects of multiple doses of mirabegron on the pharmacokinetics of digoxin. On Day 1, a single dose of 0.250 mg of digoxin (2 Lanoxin 0.125 mg tablets) was administered orally in the fasted state, and then from Day 10 to Day 23, multiple dose of 100 mg of mirabegron (one 100 mg tablet) was administered orally once daily in the fasted state. On Day 18, a single dose of 0.250 mg of digoxin was administered concomitantly with mirabegron. A total of 25 subjects received the study drug, and adverse events occurred in 11 of 25 subjects (44.0%). Adverse events reported by ≥ 2 subjects during each treatment period were palpitations in 2 of 24 subjects following administration of mirabegron alone and dysuria in 2 of 24 subjects following concomitant administration of mirabegron + digoxin. In addition, 2 subjects discontinued the study; 1 subject discontinued due to an adverse event (urticaria, which was considered to be “possibly related” to the study drug), and treatment discontinuation was decided for 1 subject by the investigator due to changes in laboratory values (AST, ALT, and CPK increased). There were no deaths. A serious adverse event in 1 subject was reported (positive for pregnancy test at the visit 1 week after the end of the study). Induced abortion was performed on this subject approximately 2 months later.

4.(iii).A.(5).18) Drug interaction study (metformin) (Attached document 5.3.3.4-7, Study No. CL-006, Study period ■ 20■ to ■ 20■, Evaluation data)

A clinical study was conducted in foreign adult male subjects at a single center in the Netherlands (target sample size, 32 subject) to investigate the drug interaction between mirabegron (IR tablets) and metformin. In the sequence A group, mirabegron 160 mg (one 100 mg tablet and two 30 mg tablets) was to be administered orally once daily in the fasted state for 16 days. From Day 12 to Day 16, metformin 500 mg (one 500 mg tablet) or placebo was to be administered orally twice daily for 5 days. In the sequence B group, metformin 500 mg was to be administered orally twice daily for 16 days. From Day 6 to Day 16, mirabegron 160 mg or placebo was to be administered orally for 11 days. Sixteen subjects were assigned to each sequence, and of these, 4 subjects were assigned to receive the placebo and 12 subjects were assigned to receive the active drug, during the concomitant administration.

A total of 32 subjects received the study drug. Adverse events occurred in 10 of 16 subjects (62.5%) following administration of mirabegron alone, in 7 of 12 subjects (58.3%) following concomitant administration of mirabegron + metformin, and in 3 of 4 subjects (75.0%) following concomitant administration of mirabegron + placebo in the sequence A group as well as 10 of 16 subjects (62.5%) following administration of metformin alone, 12 of 12 subjects (100%) following concomitant administration of metformin + mirabegron, and 4 of 4 subjects (100%) following concomitant administration of metformin + placebo in the sequence B group. Major adverse events included nervous system disorders (headache, dizziness, somnolence, dizziness postural, etc.) and gastrointestinal disorders (faeces soft, abdominal discomfort, diarrhoea NOS, nausea, abdominal pain NOS, etc.). Although there were no deaths or serious adverse events, 1 subject discontinued the study due to an adverse event (syncope) during concomitant administration of mirabegron + metformin in the sequence A group. This event was considered to be possibly related to the study drug.

4.(iii).A.(5).19) Drug interaction study (oral contraceptives) (Attached document 5.3.3.4-8, Study No. CL-068, Study period October 2008 to March 2009,

Evaluation data)

A double-blind study was conducted in healthy female subjects of childbearing potential at a single center in France (target sample size, 24 subjects) to investigate effects of mirabegron on the pharmacokinetics of oral contraceptives. The main inclusion criteria were being females of child bearing potential who had taken oral contraceptives (including 30 µg of EE and 125 µg or 150 µg of LNG) for ≥ 3 months with favorable tolerability.

The study was conducted as a 2-treatment, 2-period cross-over study. In Period 1, oral contraceptives (Minidril, 30 µg of ethinyl estradiol and 150 µg of levonorgestrel) were to be administered orally once daily for 21 days, followed by a 7-day washout period. In Period 2 after the washout period, Minidril was to be administered orally in the same manner for 21 days. In each period, mirabegron 100 mg (mirabegron 100 mg tablet) or placebo was to be administered once daily for 10 days from Day 12 of the study treatment.

A total of 30 subjects received the study drug, and of these 7 subjects discontinued the study (adverse events, 1 subject; consent withdrawal, 4 subjects; other reasons, 2 subjects). Adverse events occurred in 11 of 30 subjects, and the events reported by ≥ 2 subjects were herpes simplex in 2 of 30 subjects following administration of oral contraceptives alone, and headache in 2 of 27 subjects following concomitant administration of oral contraceptives with mirabegron, and abdominal pain in 2 of 23 subjects following concomitant administration of oral contraceptives with placebo. One subject discontinued the study due to an adverse event of urethral infection (following concomitant administration of oral contraceptives with mirabegron), of which a causal relationship to the study drug was ruled out. There were no deaths or serious adverse events.

4.(iii).A.(5).20) Thorough QT/QTc study (Attached document 5.3.4.1-1, Study No. CL-037, Study period ■ 20■ to ■ 20■, Evaluation data)

A double-blind study was conducted in healthy adult subjects at a single center in the US (target sample size, 48 subjects) to evaluate effects of multiple oral doses of 100 mg and 200 mg of mirabegron on QT interval. The study was conducted as a 4-treatment, 4-period cross-over study using 4 dosage regimens of Regimen A (2 placebo tablets for mirabegron from Day 1 to Day 6, and 2 placebo tablets for mirabegron and 1 placebo capsule for moxifloxacin on Day 7), Regimen B (1 mirabegron 100 mg tablets and 1 placebo tablet for mirabegron from Day 1 to Day 6, and 1 mirabegron 100 mg tablet, 1 placebo tablet for mirabegron, and 1 placebo capsule for moxifloxacin on Day 7), Regimen C (2 mirabegron 100 mg tablets from Day 1 to Day 6, and 2 mirabegron 100 mg tablets and 1 placebo capsule for moxifloxacin on Day 7), and Regimen D (2 placebo tablets for mirabegron from Day 1 to Day 6, and 2 placebo tablets for mirabegron and 1 moxifloxacin 400 mg capsule on Day 7). Subjects were assigned to 1 of 4 treatment sequences according to the previously defined randomization schedule. In any regimen, the study drug was to be administered in the fasted state as a single dose, a washout period of ≥ 10 days was included between the treatment periods.

A total of 48 subjects received the study drug. The incidence of adverse events reported during each study treatment period was 66.7% (32 of 48 subjects) at mirabegron 100 mg, 60.0% (27 of 45 subjects) at mirabegron 200 mg, 55.6% (25 of 45 subjects) at moxifloxacin 400 mg, and 56.5% (26 of 46 subjects) at the placebo dose. The most commonly reported adverse event was dermatitis contact in association with placement of ECG electrodes (incidence of 39.1%-47.9% during each treatment period), and the other adverse events included dysmenorrhoea (3 subjects) and anxiety (2 subjects) at the placebo dose, blood pressure increased and dysmenorrhoea (2 subjects each) at mirabegron 100 mg, headache (3 subjects), sinus tachycardia, upper respiratory tract infection, and dysmenorrhoea (2 subjects each) at mirabegron 200 mg, and dysmenorrhoea (2 subjects) at moxifloxacin 400 mg. There were no deaths. Two subjects discontinued the study treatment due to adverse events (headache, 1 subject; multiple injury associated with road traffic accident, 1 subject; both discontinued the study during Regimen B). A causal relationship to the study drug

could not be ruled out for headache (1 subject). A serious adverse event was multiple injury associated with road traffic accident in 1 subject and was considered to be unrelated to the study drug.

4.(iii).A.(5).21) Urodynamic study (Attached document 5.3.4.2-1, Study No. CL-060, Study period December 2006 to August 2008, Evaluation data)

A randomized, double-blind, parallel-group study was conducted in male patients with LUTS and BOO at 32 centers in the US and Canada (target sample size; 65 subjects per group, 195 subjects in total) to evaluate the urodynamics and safety of mirabegron.

The main inclusion criteria include being male patients aged ≥ 45 years who had urination and lower urinary tract symptoms for ≥ 3 months, the International Prostate Symptom Score (IPSS) ≥ 8 in total, and BOO Index ≥ 20 . The screening period ranged from 2 to 4 weeks after Visit 1. At Visit 2 (baseline), patients who had satisfactory screening test results and IPSS ≥ 8 in total were eligible for the study, but patients who had a total daily urine volume > 3000 mL based on the 3-day micturition diary were excluded.

Mirabegron (50 mg, 100 mg) or placebo was to be administered orally once daily after breakfast for 12 weeks.

A total of 200 subjects were enrolled and randomized (65 subjects in the placebo group, 70 subjects in the mirabegron 50 mg group, and 65 subjects in the mirabegron 100 mg group). Since all subjects orally received at least 1 dose of the study drug, 200 subjects were included in the safety analysis set. Of these, 185 subjects (63 subjects, 64 subjects, and 58 subjects, respectively) were included in the FAS for the primary efficacy analysis for urodynamic data, excluding 15 subjects (2 subjects, 6 subjects, and 7 subjects, respectively) who never provided complete urodynamic data after the study treatment. Of the safety analysis set, 2 subjects in the placebo group (both due to adverse events), 3 subjects in the 50 mg group (adverse events, 2 subjects; protocol deviation, 1 subject), and 7 subjects in the 100 mg group (adverse events, 2 subjects; protocol deviation, 1 subject; lost to follow-up, 2 subjects; other reasons, 2 subjects) discontinued the study.

Data on Q_{\max} and $P_{\det}Q_{\max}$, primary endpoints, are as shown in the table below. The lower limit of 95% CI of the difference in changes in Q_{\max} between groups (each mirabegron dose group – placebo group) exceeded -3 mL/s, the previously specified acceptable limit for non-inferiority, and the upper limit of 95% CI of the difference in changes in $P_{\det}Q_{\max}$ between groups (each mirabegron dose group – placebo group) was below 15 cm H_2O , the previously specified acceptable limit for non-inferiority.

Table. Results of the primary endpoints in the urodynamic study (FAS, Study CL-060)

		Placebo group (n = 63)	Mirabegron 50 mg group (n = 64)	Mirabegron 100 mg group (n = 58)
Q_{\max} (mL/s)	Measured values (mean \pm SD [n])			
	Baseline	7.37 \pm 3.700 (63)	7.30 \pm 3.215 (64)	7.62 \pm 3.433 (58)
	End of treatment	7.06 \pm 3.047 (63)	7.44 \pm 3.907 (64)	7.83 \pm 4.005 (58)
	Corrected mean change (end of treatment - baseline)*			
	End of treatment	-0.33 \pm 0.370 (63)	0.07 \pm 0.366 (64)	0.30 \pm 0.388 (58)
	Difference from the placebo group (95% CI)	—	0.40 [-0.63, 1.42]	0.62 [-0.43, 1.68]
$P_{\det}Q_{\max}$ (cm H ₂ O)	Measured values (mean \pm SD [n])			
	Baseline	69.56 \pm 28.468 (63)	70.72 \pm 33.689 (64)	66.95 \pm 20.694 (58)
	End of treatment	71.84 \pm 33.879 (63)	66.84 \pm 31.912 (64)	68.19 \pm 28.051 (57)
	Corrected mean change (end of treatment - baseline)*			
	End of treatment	2.92 \pm 2.906 (63)	-3.03 \pm 2.872 (64)	1.53 \pm 3.086 (57)
	Difference from the placebo group (95% CI)	—	-5.94 [-13.98, 2.09]	-1.39 [-9.73, 6.96]

* Analysis of covariance (ANCOVA) model in which the center and dose group are set as factors, and measured values at the baseline are set as a covariate.

Adverse events occurred in 28 of 65 subjects (43.1%) in the placebo group, in 28 of 70 subjects (40.0%) in the 50 mg group, and in 34 of 65 subjects (52.3%) in the 100 mg group. An adverse event with an incidence of $\geq 5\%$ in any dose group was nasopharyngitis in 4 of 70 subjects (5.7%) in the 50 mg group. There were no deaths or serious adverse events. Two subjects in the placebo group (dizziness and vertigo [1 subject each]), 1 subject in the 50 mg group (blood pressure increased), and 2 subjects in the 100 mg group (urine flow decreased and depression [1 subject each]) discontinued the study treatment due to adverse events. Depression in 1 subject in the 100 mg group was judged to be unrelated to the study drug, and the other 4 events were judged to be possibly related.

4.(iii).A.(6) Foreign phase II studies

4.(iii).A.(6).1 European late phase II studies (Attached document 5.3.5.1-5, Study No. CL-044, Study period ■ 20■■ to March 2007, Reference data)

To compare the efficacy, safety, and dose-response of mirabegron with those of the placebo and tolterodine extended-release capsules (tolterodine SR), a randomized, double-blind, parallel-group study was conducted in OAB patients at 97 centers in 14 European countries (target sample size; 140 subjects in each mirabegron dose group, 70 subjects in the tolterodine group, 770 subjects in total for evaluation [a total of 1070 subjects enrolled in the study]).

Patients who had undergone the screening test were enrolled and then given placebo during the 2-week placebo run-in period. Patients who met the inclusion criteria and did not meet the exclusion criteria were assigned to any of the placebo group, mirabegron 25 mg, 50 mg, 100 mg, and 200 mg groups, and tolterodine SR 4 mg group (assignment using the center as a stratification factor). Patients in any dose group were to orally receive the study drug once daily after breakfast for 12 weeks.

Of 1108 enrolled subjects, 928 subjects were randomized (169 subjects in the placebo group, 169 subjects in the mirabegron 25 mg group, 169 subjects in the mirabegron 50 mg group, 169 subjects in mirabegron 100 mg group, 167 subjects in mirabegron 200 mg group, and 85 subjects in the tolterodine SR 4 mg group). Of these, 927 subjects who took at least 1 dose of the study drug (169 subjects, 169 subjects, 169 subjects, 168 subjects, 167 subjects, and 85 subjects, respectively)

were included in the safety analysis set, and 919 subjects who provided data on the efficacy primary endpoints at the baseline (Visit 2) and subsequent visits (166 subjects, 167 subjects, 167 subjects, 168 subjects, 166 subjects, and 85 subjects, respectively) were included in the FAS for the primary efficacy analysis. A total of 70 subjects (12 subjects, 16 subjects, 16 subjects, 7 subjects, 16 subjects, and 3 subjects, respectively) discontinued the study and the main reasons for discontinuation were adverse events (30 subjects) and consent withdrawal (13 subjects).

Changes from baseline to the final visit in mean number of micturations per 24 hours, the efficacy primary endpoint (final visit – baseline), were as shown in the table below.

Table. Mean number of micturations (FAS, Study CL-044)

		Placebo group (n = 166)	Mirabegron 25 mg group (n = 167)	Mirabegron 50 mg group (n = 167)	Mirabegron 100 mg group (n = 168)	Mirabegron 200 mg group (n = 166)	Tolterodine SR 4 mg group (n = 85)
Baseline	Mean (SD)	11.67 (3.39)	11.87 (2.88)	11.85 (3.30)	11.81 (3.51)	11.34 (2.41)	12.31 (3.68)
Final visit	Mean (SD)	10.25 (2.82)	9.84 (2.97)	9.71 (3.33)	9.67 (3.53)	9.27 (2.90)	10.07 (3.47)
Change	Mean (SD)	-1.43 (3.24)	-2.03 (2.59)	-2.14 (2.47)	-2.14 (3.23)	-2.08 (2.67)	-2.23 (3.03)
Corrected mean change		-1.44	-1.88	-2.08	-2.12	-2.24	—
Difference from the placebo group		—	-0.45	-0.64	-0.68	-0.80	—
95% CI of the difference		—	-0.99, 0.10	-1.19, -0.10	-1.22, -0.13	-1.34, -0.25	—
P value*		—	P = 0.1083	P = 0.0205	P = 0.0152	P = 0.0041	—

* Comparison with the placebo group (ANCOVA model in which country and dose group [tolterodine group excluded] are set as factors, and measured values at the baseline are set as a covariate)

Regarding safety, the incidence of adverse events was as shown in the table below. There were no deaths.

Table. Major adverse events (safety analysis population)

	Placebo group (n = 169)	Mirabegron 25 mg group (n = 169)	Mirabegron 50 mg group (n = 169)	Mirabegron 100 mg group (n = 168)	Mirabegron 200 mg group (n = 167)	Tolterodine SR 4 mg group (n = 85)
No. of subjects with adverse event [†] (%)	73 (43.2)	74 (43.8)	74 (43.8)	77 (45.8)	80 (47.9)	41 (48.2)
Nausea	3 (1.8)	4 (2.4)	2 (1.2)	9 (5.4)	1 (0.6)	1 (1.2)
Nasopharyngitis	12 (7.1)	3 (1.8)	4 (2.4)	3 (1.8)	4 (2.4)	2 (2.4)
Urinary tract infection	5 (3.0)	11 (6.5)	3 (1.8)	2 (1.2)	4 (2.4)	3 (3.5)
No. of subjects with serious adverse event [†] (%)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	3 (1.8)	1 (1.2)

The value indicates the number of subjects (%).

Incidence of $\geq 5\%$ in any dose group

[†] Only adverse events that occurred after the study treatment were included.

4.(iii).A.(7) Foreign phase III studies

4.(iii).A.(7).1 European phase III study (Attached document 5.3.5.1-3, Study No. CL-046, Study period April 2008 to March 2009, Reference data)

A randomized, double-blind, parallel-group study was conducted in OAB patients at 189 centers in a total of 27 countries including European countries and Australia (target sample size; 430 subjects for randomized case to each group [1720 subjects in total], 2160 subjects in total for registration) to compare the efficacy and safety of mirabegron at the doses of 50 mg and 100 mg

with those of the placebo and tolterodine at the dose of 4 mg.

Patients who had undergone the screening test were enrolled and then given the placebo during a 2-week placebo run-in period. Patients who met the inclusion criteria and did not meet the exclusion criteria were assigned to any of the placebo group, mirabegron 50 mg and 100 mg, and tolterodine SR 4 mg groups (assignment using the center as a stratification factor). Patients in any dose group were to orally receive the study drug once daily with or without breakfast for 12 weeks.

Of 2437 subjects evaluated for eligibility, 2336 subjects received the placebo during the placebo run-in period. Of these, 349 subjects (ineligible case, 233 subjects; adverse events, 19 subjects; consent withdrawal, 76 subjects; etc.) discontinued the study during the placebo run-in period, and 1987 subjects were randomized (497 subjects in the placebo group, 497 subjects in the mirabegron 50 mg group, 498 subjects in the mirabegron 100 mg group, and 495 subjects in the tolterodine SR 4 mg group). Of these, 1978 subjects who took at least 1 dose of the study drug (494 subjects, 493 subjects, 496 subjects, and 495 subjects, respectively) were included in the safety analysis set, and 1906 patients who provided data on the number of micturitions at the baseline and subsequent visits by recording on the micturition diary (480 subjects, 473 subjects, 478 subjects, and 475 subjects, respectively) were included in the FAS. Of these, 1165 subjects who experienced urinary incontinence at least once at the baseline (291 subjects, 293 subjects, 281 subjects, and 300 subjects, respectively) were included in the FAS-I. Both FAS and FAS-I were the primary efficacy analysis sets. Of patients randomized, 196 subjects discontinued the study during the treatment period (44 subjects, 57 subjects, 45 subjects, and 50 subjects, respectively) and the main reasons for discontinuation were adverse events and consent withdrawal.

Regarding efficacy, significant differences were found in both change from baseline to the final visit in mean number of urinary incontinence episodes per 24 hours (final visit – baseline) and change from baseline to the final visit in mean number of micturitions per 24 hours (final visit – baseline), the primary endpoints, between either of the mirabegron 50 mg or 100 mg group and placebo group (the table below).

Table. Results of the efficacy primary endpoints (FAS and FAS-I, Study CL-046)

Mean number of urinary incontinence episodes per 24 hours at the final visit* (FAS-I)				
	Placebo group (n = 291)	Mirabegron 50 mg group (n = 293)	Mirabegron 100 mg group (n = 281)	Tolterodine SR 4 mg group (n = 300)
Baseline (mean [standard error (SE)])	2.67 (0.140)	2.83 (0.165)	2.89 (0.147)	2.63 (0.148)
Final visit (mean [SE])	1.54 (0.145)	1.22 (0.133)	1.37 (0.134)	1.42 (0.145)
Change (least squares mean [†] [SE])	–1.17 (0.113)	–1.57 (0.113)	–1.46 (0.115)	–1.27 (0.112)
Least squares mean [†] (SE) of difference in change from the placebo group (95% CI)	—	–0.41 (0.160) [–0.72, –0.09]	–0.29 (0.162) [–0.61, 0.03]	–0.10 (0.159) [–0.42, 0.21]
<i>P</i> value [†] (compared with the placebo group)	—	<i>P</i> = 0.003 [#]	<i>P</i> = 0.010 [#]	<i>P</i> = 0.11
Mean number of micturitions per 24 hours at the final visit* (FAS)				
	Placebo group (n = 480)	Mirabegron 50 mg group (n = 473)	Mirabegron 100 mg group (n = 478)	Tolterodine SR 4 mg group (n = 475)
Baseline (mean [SE])	11.71 (0.143)	11.65 (0.137)	11.51 (0.124)	11.55 (0.128)
Final visit (mean [SE])	10.35 (0.144)	9.70 (0.139)	9.76 (0.144)	9.97 (0.162)

Change (least squares mean [‡] [SE])	–1.34 (0.110)	–1.93 (0.111)	–1.77 (0.110)	–1.59 (0.111)
Least squares mean [‡] (SE) of difference in change from the placebo group (95% CI)	—	–0.60 (0.156) [–0.90, –0.29]	–0.44 (0.156) [–0.74, –0.13]	–0.25 (0.156) [–0.55, 0.06]
<i>P</i> value [‡] (compared with the placebo group)	—	<i>P</i> < 0.001 [#]	<i>P</i> = 0.005 [#]	<i>P</i> = 0.11

* Multiplicity between the 2 primary endpoints was corrected by gatekeeping procedure (Stage 1: Mean number of urinary incontinence episodes, Stage 2: Mean number of micturitions).

[†] Stratification rank ANCOVA model in which the baseline value and sex were set as covariates, and the region was set as stratum.

[‡] ANCOVA model in which the dose group, sex, and region were set as factors, and the baseline value was set as a covariate.

[#] Significantly different from the placebo group (two-sided significance level of 0.05, multiplicity in comparison between any of 2 mirabegron doses and placebo was corrected by Hochberg procedure.)

Regarding safety, adverse events occurred in 214 of 494 subjects (43.3%) in the placebo group, 211 of 493 subjects (42.8%) in the mirabegron 50 mg group, 199 of 496 subjects (40.1%) in the mirabegron 100 mg group, and 231 of 495 subjects (46.7%) in the tolterodine SR 4 mg group. Of these, adverse events reported by $\geq 5\%$ of subjects in any group included hypertension (38 subjects [7.7%], 29 subjects [5.9%], 27 subjects [5.4%], and 40 subjects [8.1%], respectively) and dry mouth (13 subjects [2.6%], 14 subjects [2.8%], 14 subjects [2.8%], and 50 subjects [10.1%], respectively). One subject in the tolterodine SR 4 mg group died of ruptured cerebral aneurysm, which was considered to be possibly or probably related to the study drug. Serious adverse events occurred in 8 subjects (1.6%) in the placebo group, 14 subjects (2.8%) in the mirabegron 50 mg group, 12 subjects (2.4%) in the mirabegron 100 mg group, and 11 subjects (2.2%) in the tolterodine SR 4 mg group. Of these, serious adverse events considered to be possibly or probably related to the study drug included 6 events in 4 subjects of the placebo group (atrioventricular block first degree, chest pain, myocardial infarction, pyrexia, asthenia, and balance disorder), 4 events in 3 subjects of the mirabegron 50 mg group (hypertensive crisis, acute coronary syndrome, abdominal pain, and hepatic enzyme increased), 3 events in 2 subjects of the mirabegron 100 mg group (atrial fibrillation, cardiac failure acute, and cerebral ischaemia), and 7 events in 6 subjects of the tolterodine group (arrhythmia, fall, ruptured cerebral aneurysm, hypertension, leukaemia, gastritis, and hepatitis). The incidence of adverse events leading to treatment discontinuation was 2.6%, 4.9%, 3.2%, and 4.4% in the placebo group, mirabegron 50 mg group, mirabegron 100 mg group, and tolterodine SR 4 mg group, respectively.

4.(iii).A.(7).2) US phase III study (Attached document 5.3.5.1-4, Study No. CL-047, Study period ■ 2008 to April 2009, Reference data)

A randomized, double-blind, parallel-group study was conducted in OAB patients at 115 centers in the US and at 17 centers in Canada (target sample size; 430 subjects for randomized case to each group [1290 subjects in total], 1620 subjects in total for registration) to compare the efficacy and safety of mirabegron at the doses of 50 mg and 100 mg with those of the placebo.

Patients who had undergone the screening test were enrolled and then given the placebo during a 2-week placebo run-in period. Patients who met the inclusion criteria and did not meet the exclusion criteria were assigned to any of the placebo group, mirabegron 50 mg group, and mirabegron 100 mg group (assignment using the center as a stratification factor). Patients in any dose group were to orally receive the study drug once daily with or without breakfast for 12 weeks.

Of 2342 subjects evaluated for eligibility, 2149 subjects received the placebo during the placebo run-in period. Of these, 820 subjects (ineligible case, 568 subjects; adverse events, 21 subjects; consent withdrawal, 157 subjects; etc.) discontinued the study during the placebo run-in period,

and 1329 subjects were randomized (454 subjects in the placebo group, 442 subjects in the mirabegron 50 mg group, and 433 subjects in the mirabegron 100 mg group). Of these, 1328 subjects who took the study drug at least once (453 subjects, 442 subjects, and 433 subjects, respectively) were included in the safety analysis set, and 1270 subjects who provided data on the number of micturitions at the baseline and subsequent visits by recording on the bladder diary (433 subjects, 425 subjects, and 412 subjects, respectively) were included in the FAS. Of these, 933 subjects who experienced urinary incontinence at least once at the baseline (325 subjects, 312 subjects, and 296 subjects, respectively) were included in the FAS-I. Both FAS and FAS-I were the primary efficacy analysis set. Of subjects randomized, 181 subjects discontinued the study during the treatment period (69 subjects, 59 subjects, and 53 subjects, respectively) and the main reasons for discontinuation were consent withdrawal and adverse events.

Regarding efficacy, significant differences were found in both change from baseline to the final visit in mean number of urinary incontinence episodes per 24 hours (final visit – baseline) and change from baseline to the final visit in mean number of micturitions per 24 hours (final visit – baseline), the primary endpoints, between either of the mirabegron 50 mg or 100 mg group and placebo group (the table below).

Table. Results of the efficacy primary endpoints (FAS and FAS-I, Study CL-047)

Mean number of urinary incontinence episodes per 24 hours at the final visit* (FAS-I)			
	Placebo group (n = 325)	Mirabegron 50 mg group (n = 312)	Mirabegron 100 mg group (n = 296)
Baseline (mean [SE])	3.03 (0.171)	2.77 (0.150)	2.69 (0.142)
Final visit (mean [SE])	1.81 (0.152)	1.33 (0.133)	1.14 (0.128)
Changes (least squares mean [†] [SE])	–1.13 (0.112)	–1.47 (0.114)	–1.63 (0.117)
Least squares mean [‡] (SE) of difference in change from the placebo group (95% CI)	—	–0.34 (0.160) [–0.66, –0.03]	–0.50 (0.162) [–0.82, –0.18]
<i>P</i> value [‡] (compared with the placebo group)	—	<i>P</i> = 0.026 [#]	<i>P</i> < 0.001 [#]
Mean number of micturitions per 24 hours at the final visit* (FAS)			
	Placebo group (n = 433)	Mirabegron 50 mg group (n = 425)	Mirabegron 100 mg group (n = 412)
Baseline (mean [SE])	11.51 (0.157)	11.80 (0.168)	11.66 (0.167)
Final visit (mean [SE])	10.51 (0.164)	10.09 (0.175)	9.91 (0.166)
Change (least squares mean [‡] [SE])	–1.05 (0.132)	–1.66 (0.133)	–1.75 (0.135)
Least squares mean [‡] (SE) of difference in change from the placebo group (95% CI)	—	–0.61 (0.188) [–0.98, –0.24]	–0.70 (0.189) [–1.07, –0.33]
<i>P</i> value [‡] (compared with the placebo group)	—	<i>P</i> = 0.001 [#]	<i>P</i> < 0.001 [#]

* Multiplicity between the 2 primary endpoints was corrected by gatekeeping procedure (Stage 1: Mean number of urinary incontinence episodes, Stage 2: Mean number of micturitions).

[†] Stratification rank ANCOVA model in which the baseline value and sex were set as covariates, and the region was set as stratum.

[‡] ANCOVA model in which the dose group, sex, and region were set as factors, and the baseline value was set as a covariate.

[#] Significantly different from the placebo group (two-sided significance level of 0.05, multiplicity in comparison between any of 2 mirabegron doses and placebo was corrected by Hochberg procedure.)

Regarding safety, adverse events occurred in 227 of 453 subjects (50.1%) in the placebo group, 228 of 442 subjects (51.6%) in the mirabegron 50 mg group, and 203 of 433 subjects (46.9%) in the mirabegron 100 mg group. Of these, an adverse event reported by ≥5% of subjects in any group was hypertension (30 subjects [6.6%], 27 subjects [6.1%], and 21 subjects [4.9%],

respectively). Death occurred in 1 subject each in the placebo group and 100 mg group (2 subjects in total).

The incidence of serious adverse events was 2.0% (9 of 453 subjects), 2.5% (11 of 442 subjects), and 3.2% (14 of 433 subjects), respectively. Serious adverse events considered to be possibly or probably related to the study drug included 3 events in 3 subjects of the mirabegron 50 mg group (gastroenteritis, pneumonia, and atrial fibrillation) and 1 event in 1 subject of the mirabegron 100 mg group (supraventricular tachycardia). Subjects who discontinued the study due to adverse events accounted for 2.2%, 2.5%, and 2.8%, respectively.

4.(iii).A.(7).3 Foreign long-term treatment study (Attached document 5.3.5.1-6, Study No. CL-049, Study period April 2008 to May 2010, Reference data)

A randomized, double-blind, parallel-group study was conducted in OAB patients at 306 centers overseas (target sample size, approximately 2500 subjects for enrollment) to investigate the safety and efficacy following long-term treatment of mirabegron at the dose of 50 mg or 100 mg, or tolterodine ER at the dose of 4 mg.

The study was to include not only patients who completed Study CL-046 and Study CL-047 but also patients who did not participate in either study. Patients who had undergone the screening test were enrolled and then given the placebo during a 2-week placebo run-in period. Patients who met the inclusion criteria and did not meet the exclusion criteria were randomly assigned to any of the mirabegron 50 mg and 100 mg, and tolterodine SR 4 mg groups (assignment using the center as a stratification factor), and patients in any dose group were to orally receive the study drug once daily with or without breakfast for 52 weeks.

Of 2849 subjects evaluated for eligibility, 2801 subjects received the placebo during the placebo run-in period. Of these, 2452 subjects were randomized (815 subjects in mirabegron 50 mg group, 824 subjects in mirabegron 100 mg group, and 813 subjects in the tolterodine SR 4 mg group). Of these, 2444 subjects who took at least 1 dose of the study drug (812 subjects, 820 subjects, and 812 subjects, respectively) were included in the safety analysis set, and 2382 subjects who provided data on the number of micturitions at the baseline and subsequent visits by recording on the micturition diary (789 subjects, 802 subjects, and 791 subjects, respectively) were included in the FAS. Of these, 1450 subjects who experienced urinary incontinence at least once at the baseline (479 subjects, 483 subjects, and 488 subjects, respectively) were included in the FAS-I. Both FAS and FAS-I were the primary efficacy analysis populations. Of subjects randomized, 557 subjects discontinued the study during the treatment period (186 subjects, 179 subjects, and 192 subjects, respectively) and the main reasons for discontinuation were consent withdrawal, adverse events, and lack of efficacy.

Regarding safety, the incidence of adverse events was as shown in the table below.

Table. Adverse events (safety analysis population, Study CL-049)

Parameter	Mirabegron 50 mg group (n = 812)	Mirabegron 100 mg group (n = 820)	Tolterodine SR 4 mg group (n = 812)
Any adverse events reported	485 (59.7)	503 (61.3)	508 (62.6)
Hypertension	75 (9.2)	80 (9.8)	78 (9.6)
Urinary tract infection	48 (5.9)	45 (5.5)	52 (6.4)
Dry mouth	23 (2.8)	19 (2.3)	70 (8.6)
Serious adverse events	42 (5.2)	51 (6.2)	44 (5.4)
Adverse events leading to treatment discontinuation	48 (5.9)	50 (6.1)	46 (5.7)

The value indicates the number of subjects (%).

Incidence of $\geq 5\%$ in any group

Deaths occurred in 3 subjects in the mirabegron 50 mg group (cardiac failure, multi-organ failure associated with sepsis, pneumonia, and completed suicide) and in 2 subjects in the tolterodine group (coronary artery disease, cerebrovascular accident, and pneumonia aspiration). The relationships to the study drug were not ruled out for pneumonia and completed suicide in the mirabegron 50 mg group. Serious adverse events considered to be possibly or probably related to the study drug included 16 events in 11 subjects of the mirabegron 50 mg group (atrial fibrillation and myocardial ischaemia, 2 events each; difficulty in walking, cardiac arrest, myocardial infarction, ventricular fibrillation, ventricular tachycardia, gastritis, atrioventricular block first degree, completed suicide, open angle glaucoma, urticaria, cellulitis, and atrial flutter, 1 event each), 7 events in 4 subjects of the mirabegron 100 mg group (liver function test abnormal, 3 events; haemolytic anaemia, thrombocytopenia, angle closure glaucoma, and coronary artery disease, 1 event each), and 7 events in 4 subjects of the tolterodine group (atrial fibrillation, 2 events; dehydration, renal failure acute, angina pectoris, ischaemia, and myocardial infarction, 1 event each).

Regarding efficacy, the number of urinary incontinence episodes was decreased from the baseline in any dose group; the mean number of urinary incontinence episodes per 24 hours (mean \pm SE) was changed from 2.66 ± 0.120 at the baseline to 1.61 ± 0.130 at the final visit in the mirabegron 50 mg group, from 2.49 ± 0.113 to 1.26 ± 0.104 in the mirabegron 100 mg group, and from 2.42 ± 0.107 to 1.19 ± 0.094 in the tolterodine SR 4 mg group. The number of micturitions was also decreased in any dose group; the mean number of micturitions per 24 hours (mean \pm SE) was changed from 11.13 ± 0.100 at the baseline to 9.85 ± 0.110 at the final visit in the mirabegron 50 mg group, from 11.16 ± 0.102 to 9.73 ± 0.113 in the mirabegron 100 mg group, and from 10.94 ± 0.093 to 9.58 ± 0.109 in the tolterodine SR 4 mg group.

4.(iii).B. Outline of the review by PMDA

4.(iii).B.(1) Efficacy

4.(iii).B.(1).1 Study designs of Study CL-045 and Study CL-048

The applicant explained the efficacy endpoints and comparator in the Japanese phase II study (Study CL-045) and Japanese phase III study (Study CL-048) as follows:

The “Guideline for Clinical Evaluation Methods of Therapeutic Drugs for Overactive Bladder” (PFSB/ELD Notification No. 0628001 dated June 28, 2006) recommends including number of micturitions and/or number of urinary incontinence episodes based on the micturition diary records in studies as observation items appropriate for efficacy evaluation, the mean number of micturitions per 24 hours and number of urinary incontinence episodes per 24 hours were selected as the primary and secondary endpoints, respectively, in Study CL-045 and Study CL-048, and the obtained data were evaluated.

Both Study CL-045 and Study CL-048 were placebo-controlled to investigate superiority of mirabegron to the placebo for efficacy evaluation. Furthermore, in Study CL-048, tolterodine (4 mg/day), a therapeutic drug for treatment of OAB that was approved in both Japan and overseas and most commonly used in Europe and the US, was included as the comparator to investigate clinical positioning of mirabegron. This study was designed to compare the efficacy and safety among treatment groups, but not to compare mirabegron with tolterodine statistically.

PMDA considers as follows:

Designs of both Study CL-045 and Study CL-048 were appropriate in the following points: (i) number of micturitions, number of urinary incontinence episodes, and number of urge urinary incontinence episodes were set as the efficacy endpoints and the studies were placebo-controlled to investigate the efficacy of mirabegron and (ii) as the mirabegron dose, 50 mg was selected in Study CL-048 (the appropriateness of the dose selection are presented in “4.(iii).B.(5).1) Dosage”). Since a confirmatory study of mirabegron should compare mirabegron with existing

therapeutic drugs for OAB to obtain information facilitating investigation of clinical positioning of mirabegron, it is appropriate to include tolterodine (4 mg), a commonly used therapeutic drug for OAB. While existing drugs indicated for OAB have anticholinergic actions, mirabegron is expected to alleviate OAB through a mechanism of action different from that of the anticholinergic action. In consideration of the above, the design of the confirmatory study, which was not intended to evaluate non-inferiority of mirabegron to tolterodine, is acceptable.

4.(iii).B.(1).2) Efficacy in Study CL-045 and Study CL-048

To investigate the efficacy and dose-response of mirabegron at the doses of 25 mg, 50 mg, and 100 mg using the placebo as a comparator, Study CL-045 included not only the change in mean number of micturitions as the primary endpoint but also changes in mean number of urinary incontinence episodes and mean number of urge urinary incontinence episodes as the secondary endpoints. As a result, all mirabegron dose groups showed improvement in all of these endpoints with significant differences from the placebo group. In addition, a significant difference was found in change in mean number of urgency episodes between the mirabegron 100 mg group and placebo group.

In the confirmatory study, Study CL-048, changes in all of the mean number of micturitions, mean number of urinary incontinence episodes, mean number of urgency episodes, and mean number of urge urinary incontinence episodes showed improvement in the mirabegron 50 mg group compared with the placebo group and there were significant differences between the 2 groups. Although the interpretation of the data has limitations due to absence of statistical comparisons, the study showed no marked difference in efficacy between the mirabegron 50 mg group and tolterodine 4 mg group.

Based on the above results from Study CL-045 and Study CL-048, PMDA has concluded that the efficacy of mirabegron 50 mg in patients with OAB was confirmed. The appropriateness of the dosage regimen set in the studies and of recommended clinical dose of mirabegron are discussed in “4.(iii).B.(5) Dosage and administration.”

4.(iii).B.(1).3) Efficacy in Study CL-051

PMDA considers as follows:

Study CL-051, which was conducted as a Japanese long-term treatment study, was designed to allow the mirabegron dose to be increased from 50 mg to 100 mg when the investigator judged that the effect of the therapeutic drug at the dose of 50 mg was insufficient at the first evaluation at Week 8, and the dose increase would not cause safety issues. At Week 8, of 203 subjects treated with mirabegron, 145 subjects maintained the dose at 50 mg, 50 subjects had the dose increased to 100 mg, and 8 subjects discontinued the study before dose adjustment at Week 8. The efficacy endpoints (mean number of micturitions, mean number of urgency episodes, mean number of urinary incontinence episodes) showed almost constant improvement in subjects at the maintenance dose of 50 mg from Week 8 to Week 52 (the final visit). PMDA has concluded that the efficacy will not be attenuated during the mirabegron 50 mg long-term treatment.

The applicant explained that changes in the major micturition parameters in subjects at the increased dose of 100 mg demonstrated the effects of the increased dose, since the dose escalation due to insufficient response at Week 8 led to the improvements in these parameters. However, PMDA considers that the effects of the increased dose to 100 mg cannot be evaluated only based on the study data because this study was designed as an open-label uncontrolled study, which did not allow the effects to be evaluated separately from the placebo effect associated with the dose increase. The usefulness of the dose increase to 100 mg is further discussed in “4.(iii).B.(5) Dosage and administration” section.

4.(iii).B.(2) Safety

4.(iii).B.(2).1) Adverse events in clinical studies

The applicant explained adverse events in the Japanese clinical studies as follows:

(a) Commonly observed adverse events

According to the combined data from Study CL-045 and Study CL-048, the incidence of adverse events was 76.0% (449 of 591 subjects) in the placebo group, 80.5% (169 of 210 subjects) in the mirabegron 25 mg group, 77.0% (452 of 587 subjects) in the mirabegron 50 mg group, 84.1% (175 of 208 subjects) in the mirabegron 100 mg group, and 81.3% (305 of 375 subjects) in the tolterodine group, showing that the incidence in the 100 mg group was slightly higher than those in the other groups. The incidence in any of the mirabegron dose groups was not considerably different from that in the placebo group and was comparable to that in the tolterodine group. Adverse events in all of the subjects treated with mirabegron (all doses of 25, 50, and 100 mg) were analyzed by event. As a result, adverse events with an incidence of $\geq 5\%$ were blood glucose increased (19.7%), nasopharyngitis (18.7%), urinary sediment abnormal (12.7%), blood creatine phosphokinase increased (12.5%), gamma-glutamyltransferase increased (10.1%), protein urine present (9.4%), and glucose urine present (5.3%), most of which were classified into Investigations of system organ class (SOC). These events also occurred at comparable incidences in the placebo group. There were no noteworthy differences between mirabegron and placebo. Although dry mouth occurred at a higher incidence in the tolterodine group than in the placebo group, the incidence in any of the mirabegron doses group was comparable to that in the placebo group. The incidence was not increased with increasing dose.

In Study CL-051, the incidence of adverse events was 67.8% (137 of 202 subjects) during the initial study treatment period until Week 8 and 93.6% (189 of 202 subjects) throughout the study treatment period (from the baseline to Week 52). The common adverse events after dose increase (Week 8) were mostly classified into Gastrointestinal disorders, Infections and infestations, and Investigations of SOC. The incidence with or without the dose increase was 91.4% (139 of 152 subjects) in subjects at the maintenance dose of 50 mg and 100% (50 of 50 subjects) in subjects at the increased dose of 100 mg. Adverse events with an incidence of $\geq 5\%$ across all subjects were blood glucose increased (30.7%), nasopharyngitis (29.7%), urinary sediment abnormal (23.3%), blood creatine phosphokinase increased (20.3%), gamma-glutamyltransferase increased (10.9%), cystitis (7.9%), white blood cell count decreased (7.4%), protein urine present (7.4%), glucose urine present (6.4%), constipation (5.4%), blood cholesterol increased (5.4%), and alanine aminotransferase increased (5.0%). Subjects both at the maintenance dose of 50 mg and at the increased dose of 100 mg experienced similar types of adverse events at comparable frequencies. The incidence of adverse events by timing of the onset was 67.8% (137 of 202 subjects) from Week 1 to Week 8 (Days 1-56), 34.9% (68 of 195 subjects) from Week 9 to Week 16 (Days 57-112), 42.1% (80 of 190 subjects) from Week 17 to Week 28 (Days 113-196), 52.2% (96 of 184 subjects) from Week 29 to Week 40 (Days 197-280), and 43.3% (74 of 171 subjects) from Week 41 onward (\geq Day 281), and the incidence did not tend to increase with long-term treatment. Analysis of the adverse events by event did not show any trend of development of additional adverse events due to long-term treatment.

Adverse events that occurred at all mirabegron doses (25 mg, 50 mg, 100 mg) in the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051) were subjected to analysis to identify factors affecting the incidence. As a result, sex, age, and body weight were not identified as factors affecting the incidence at any dose.

(b) Deaths and serious adverse events

Of OAB patients treated with mirabegron in the Japanese clinical studies, death occurred in 1 subject at the increased dose of 100 mg (female aged 59 years) in Study CL-051. The cause of death was aortic dissection and it was inferred that the subject died within several minutes after the onset of aortic dissection. This subject had gastritis and pollinosis concurrently, but did not have other prior or concurrent disease. Although the blood pressure of the subject was slightly

high before and after treatment with mirabegron, which changed within an acceptably small fluctuation range, no abrupt increase was observed. The investigator judged that the causal relationship to mirabegron “could be ruled out” for aortic dissection because no symptoms or signs suggesting the onset of the event were noted before and after treatment with mirabegron, nor were any remarkably abnormal values or changes found in clinical laboratory values. On the other hand, the sponsor judged that the relationship “could not be completely ruled out” since the death was confirmed on arrival at the hospital, lacking the information related to the subject at the onset of the event.

According to results of the analysis on combined data from Study CL-045 and Study CL-048, the incidence of serious adverse events was low in all dose groups, the incidence in the placebo group, mirabegron 25 mg, 50 mg, and 100 mg groups, and tolterodine group was 1.4% (8 of 591 subjects), 1.4% (3 of 210 subjects), 0.7% (4 of 587 subjects), 0.5% (1 of 208 subjects), and 1.1% (4 of 375 subjects), respectively, and the incidences in the mirabegron dose groups were comparable to that in the placebo group. The incidence of serious adverse events in Study CL-051 was 3.5% (7 of 202 subjects) (2.6% [4 of 152 subjects] in subjects at the maintenance dose of 50 mg, 6.0% [3 of 50 subjects] in subjects at the increased dose of 100 mg). In the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), a total of 15 subjects in the mirabegron groups experienced serious adverse events (ischaemic colitis, colonic polyp, appendicitis, pneumonia primary atypical, pyelonephritis acute, clavicle fracture, patella fracture, spinal compression fracture, basal cell carcinoma, malignant anorectal neoplasm, ovarian neoplasm, cerebral haemorrhage, cerebral infarction, Stevens-Johnson syndrome, aortic dissection). Of these, the serious adverse events of which a causal relationship to the study drug could not be ruled out were anaemia and loss of consciousness in the placebo group, cerebral haemorrhage in the mirabegron 25 mg group, Stevens-Johnson syndrome in the mirabegron 100 mg group, and colitis in the tolterodine group. All of these events resolved except for cerebral haemorrhage, which was resolving. Compared with serious adverse events in European Phase III study (Study CL-046) and US Phase III study (Study CL-047), no trend of developing specific serious adverse events was observed.

(c) Adverse events leading to treatment discontinuation

According to results of the analysis on combined data from Study CL-045 and Study CL-048, the incidence of adverse events leading to treatment discontinuation was 2.0% (12 of 591 subjects) in the placebo group, 2.4% (5 of 210 subjects) in the mirabegron 25 mg group, 3.2% (19 of 587 subjects) in the mirabegron 50 mg group, 3.8% (8 of 208 subjects) in the mirabegron 100 mg group, and 3.2% (12 of 375 subjects) in the tolterodine group. In Study CL-051, the incidence of such events was 7.4% (15 of 202 subjects) (6.6% [10 of 152 subjects] in subjects at the maintenance dose of 50 mg, 10.0% [5 of 50 subjects] in subjects at the increased dose of 100 mg). Of the adverse events leading to treatment discontinuation in the mirabegron dose groups, headache and hypertension occurred at the incidence of 0.2% (3 of 1207 subjects), and the incidence of other events was <0.2%.

PMDA evaluated the safety of mirabegron mainly based on the data from Study CL-045 and Study CL-048. As a result, taking account of the incidence of adverse events in the clinical studies, there was no trend that specific adverse events occurred more frequently in the mirabegron dose groups than in the placebo and tolterodine groups. Therefore, PMDA considers that mirabegron is tolerated. In addition, PMDA considers that the data from Study CL-051 indicated no adverse events caused due to the long-term treatment. The cardiovascular risk potentially related to the pharmacological action of mirabegron is discussed in the following section.

4.(iii).B.(2).2) Cardiovascular risk

(a) QT/QTc prolongation and arrhythmogenic potential

Taking into account that non-clinical studies (safety pharmacology) showed that unchanged

mirabegron as well as the plasma metabolites, M5, M14, and M16, inhibited hERG current, and the thorough QT/QTc study (Study CL-037) showed that mirabegron may have induced QT prolongation, PMDA asked the applicant to explain the QT/QTc prolongation and arrhythmogenic potential induced by mirabegron in Japanese patients in consideration of Japanese and foreign clinical data and the interim data from the additional thorough QT/QTc study submitted after the application.

The applicant responded as follows:

Since the exploratory re-analysis performed in the thorough QT/QTc study (Study CL-037) suggested the effect on QTc interval, the FDA directed the applicant that the effect should be further investigated. In accordance with the FDA's direction, the additional thorough QT/QTc study (Study CL-077; target sample size, 352 subjects; mirabegron doses, 50, 100, 200 mg) was conducted. The upper limit of 90% CI of ddQTcI at the doses of 50, 100, and 200 mg in the overall study population did not exceed 10 ms. In the subgroup analysis by sex, the upper limit of 90% CI of ddQTcI at the doses of 50, 100, and 200 mg in male subjects did not exceed 10 ms. The upper limit of 90% CI of ddQTcI at the doses of 50 and 100 mg in female subjects did not exceed 10 ms, but the upper limit of 90% CI at the dose of 200 mg exceeded 10 ms at 0.5, 1.5 to 6, and 10 hours post-dose (maximum effect, 10.42 ms at 5 hours [two-sided 90% CI, 7.40-13.44]). On the other hand, categorical analysis on QTcI interval and its changes from the baseline at the doses of 50, 100, and 200 mg did not identify any subject of either sex in whom the QTcI interval exceeded 480 ms and its change from the baseline exceeded 60 ms. QTcI interval >450 ms was found in female subjects, the incidence was 4.9% (2 of 41 subjects) at 50 mg, 2.6% (1 of 38 subjects) at 100 mg, and 13.5% (5 of 37 subjects) at 200 mg. The change in QTcI interval from the baseline >30 ms was not found in any subject at the doses of 50 and 100 mg but was found in 5.4% (2 of 37 subjects) of the female subjects at the dose of 200 mg. Based on the above, results from the additional thorough QT/QTc study (Study CL-077) were consistent with the thorough QT/QTc study (Study CL-037).

Regarding the safety of mirabegron related to QTc interval based on the Japanese clinical data, in Study CL-045, the mean change in QTc interval measured using 12-lead electrocardiogram (II-lead) and corrected by Fridericia formula was 2.88 ms in the placebo group, 1.93 ms in the mirabegron 25 mg group, 4.48 ms in the mirabegron 50 mg group, and 3.22 ms in the mirabegron 100 mg group. The analysis did not identify any subject with the change in QTc interval >60 ms or any group with "clinically significant prolongation" of QTc interval >500 ms as described in "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (PFSB/ELD Notification No. 1023-1 dated October 23, 2009, ICH E14 guideline). The analysis for relationship between the QTc change from the baseline to the final visit (Δ QTc) and plasma concentration of unchanged mirabegron failed to show the Δ QTc prolongation with increasing plasma concentration of unchanged mirabegron. In addition, exploratory logistic regression analysis failed to show any relationship between the frequency of Δ QTc prolongation >30 ms and the plasma concentration of unchanged mirabegron. As described above, analyses for concentration-QTc correlation in Study CL-045 did not show any relationship between the plasma mirabegron concentration and QTc interval prolongation effect.

To identify adverse events with a proarrhythmic potential or those related to QTc prolonged in the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), adverse events under a category of "Torsade de pointes (TdP)/QT prolonged" were extracted according to the standardized MedDRA query (SMQ) (electrocardiogram QT prolonged, TdP, long QT syndrome congenital, electrocardiogram QT interval abnormal, ventricular tachycardia, long QT syndrome, cardio-respiratory arrest, loss of consciousness, sudden death, syncope, ventricular arrhythmia, cardiac arrest, ventricular flutter, cardiac death, electrocardiogram repolarisation abnormality, electrocardiogram U-wave abnormality, electrocardiogram U-wave biphasic, cardiac fibrillation, ventricular tachyarrhythmia, sudden cardiac death, ventricular fibrillation). As a result, the extracted

adverse event was only loss of consciousness reported by 1 subject in the placebo group of Study CL-048, and there was no such event in subjects treated with mirabegron.

In the European Phase III study (Study CL-046), QTc interval at the final visit >500 ms was found in 1 subject in the 100 mg group (0.2%), but the subject did not experience adverse events related to QTc prolongation. In subjects treated with mirabegron, the incidences of QTc interval >480 ms or >450 ms and of QTc interval prolongation of ≥ 30 ms were comparable to those in the placebo group. QTc interval prolongation of ≥ 60 ms was found in 1 subject each in the placebo group and mirabegron 50 mg group and in 2 subjects in the mirabegron 100 mg group. Even in the US Phase III study (Study CL-047), the incidences of QTc interval >480 ms or >450 ms and of QTc interval prolongation of ≥ 30 ms in subjects treated with mirabegron were comparable to those in the placebo group. No QTc interval prolongation of ≥ 60 ms was found in any group. No adverse events related to QTc prolongation were extracted from adverse events in a total of 1864 subjects treated with mirabegron at the doses of 50 mg and 100 mg in the above 2 foreign clinical studies according to the SMQ.

Mirabegron is considered to be a drug insensitive to ethnic factors, and the difference in plasma concentration between Japanese and foreign patients can be explained by the difference in body weight, the applicant determined that it is possible to use data from the foreign thorough QT/QTc study for the risk evaluation in Japanese patients.

In addition, the applicant explained the cautions for the risk of mirabegron-induced QT prolongation in the package insert as follows:

Based on the investigation results, mirabegron-induced QTc prolongation is unlikely to cause clinical problems, but possible additive effect of overdosed mirabegron cannot be ruled out in patients with long QT syndrome or patients on medication causing QT prolonged in post-marketing practices. Therefore, the safety caution statement that “Patients with long QT syndrome or patients on medication causing QT prolonged should be cautioned against overdosage” will be included in the “Important Precautions” section in the package insert (draft).

PMDA considers the risk of QT prolonged of mirabegron as follows:

In clinical studies both in Japan and overseas, no adverse events potentially related to TdP and QT prolonged were observed in patients treated with mirabegron, but the data from Study CL-037 and Study CL-077 showed that mirabegron caused QT prolonged in female patients in a concentration dependent manner. Therefore, the risk of QT prolonged in female patients at high doses of mirabegron cannot be ruled out. That is, overall data both from Study CL-037 and Study CL-077 did not meet the criteria for positive results in the ICH E14 guideline, and the subgroup analysis results by sex have to be interpreted with caution. Especially, PMDA cannot underestimate the fact that the risk of QT prolongation was reproducibly indicated especially in female patients at the mirabegron dose ≥ 200 mg. Although the applicant claims that mirabegron is considered to be a drug insensitive to ethnic factors, and that the difference in plasma concentration between Japanese and foreign patients can be explained by the difference in body weight, PMDA determines that the plasma mirabegron concentrations are higher in Japanese patients than in foreign patients. Although no adverse events potentially related to TdP and QT prolongation were reported in the clinical studies in Japan or overseas, these studies included only a limited number of patients with limited demographics. Once approved, mirabegron may be administered to patients with various demographics in clinical practice (including patients with latency long QT syndrome). It cannot be ruled out that adverse events related to QT prolonged may occur during mirabegron treatment.

Based on the above, PMDA considers it necessary to include adequate cautions for the risk of QT prolonged of mirabegron in the package insert. The current package insert (draft) submitted by the applicant includes in the “Important Precautions” section a caution “Patients with long QT

syndrome or patients on medication causing QT prolongation should be cautioned against overdosage.” However, mirabegron may cause QT prolongation even when used within the range of the proposed dosage, depending on patient demographics and interaction with the concomitant drugs. PMDA thus considers it necessary to provide explicit cautions. For instance, the “Careful Administration” section includes patients with long QT syndrome, patients on medication known to cause QT prolongation (including anti-arrhythmia potassium channel blockers), patients with underlying cardiac disease or with hypokalemia at a high risk of QT prolongation. In addition, the applicant should consider whether or not the following caution needs to be provided in the “Important Precautions” section, “QT prolonged associated with mirabegron may occur. For patients with cardiovascular diseases, caution should be exercised to the cardiovascular conditions before starting the treatment with mirabegron.” Furthermore, it is desirable to provide specific information about the data from Study CL-037 and Study CL-077 in terms of the risk of mirabegron-induced QT prolongation, including the finding that the risk may differ between male and female patients. In addition, it is essential to collect information about adverse events related to QT prolongation and TdP through a post-marketing surveillance. The details of the cautions about the risk of mirabegron-induced QT prolongation in the package insert (including necessity of periodic ECG examinations) and post-marketing information collection will be further reviewed, taking also account of comments raised in the Expert Discussion.

(b) Other cardiovascular adverse events

The pharmacological action of mirabegron is based on its agonistic effect on β_3 -adrenoceptors, generating concern about the cardiovascular risk. PMDA asked the applicant to explain their views on the cardiovascular risk in patients treated with mirabegron.

The applicant explained as follows:

Cardiovascular adverse events (adverse events classified into Cardiac disorders, Investigations [related to ECG and blood pressure], and Vascular disorders under MedDRA/J Version 12.1 SOC) in Study CL-045, Study CL-048, and Study CL-051 were analyzed by patient demographic factors.

Analysis on cardiovascular adverse events in Study CL-045 and Study CL-048 by age (elderly subjects [aged ≥ 65 years] or non-elderly subjects [aged < 65 years]) showed that the incidences in non-elderly subjects in the placebo group, the mirabegron 25 mg group, the mirabegron 50 mg group, the mirabegron 100 mg group, and the tolterodine group were 3.1% (12 of 381 subjects), 2.0% (3 of 147 subjects), 1.6% (6 of 376 subjects), 3.7% (5 of 135 subjects), and 2.6% (6 of 228 subjects), while the incidence in elderly patients was 4.8% (10 of 210 subjects), 7.9% (5 of 63 subjects), 7.1% (15 of 211 subjects), 8.2% (6 of 73 subjects), and 8.8% (13 of 147 subjects), respectively. The incidences in elderly subjects were higher than those in non-elderly subjects, but in elderly subjects, the incidences in the mirabegron dose groups were comparable to that in the placebo group. In addition, analysis on cardiovascular adverse events in Study CL-051 by age showed that the incidences in non-elderly subjects at the maintenance dose of 50 mg and subjects at the increased dose of 100 mg were 10.4% (11 of 106 subjects) and 18.2% (6 of 33 subjects), respectively, while the incidences in elderly patients at the maintenance dose of 50 mg and patients at the increased dose of 100 mg were 23.9% (11 of 46 subjects) and 11.8% (2 of 17 subjects), respectively. The incidence of each cardiovascular adverse event was not largely different between elderly and non-elderly subjects. There were no cardiovascular adverse events of which incidence was increased following the dose increase or long-term treatment in elderly subjects.

Analysis on cardiovascular adverse events in Study CL-045 and Study CL-048 by concurrent hypertension (whether or not hypertension was listed in the medical record as a concurrent disease) showed that the incidences in non-hypertensive subjects in the placebo group, the mirabegron 25 mg, the mirabegron 50 mg group, the mirabegron 100 mg group and the tolterodine

group were 3.4% (15 of 441 subjects), 3.4% (6 of 174 subjects), 2.4% (11 of 456 subjects), 5.2% (8 of 153 subjects), and 3.0% (8 of 268 subjects), while the incidence in hypertensive patients was 4.7% (7 of 150 subjects), 5.6% (2 of 36 subjects), 7.6% (10 of 131 subjects), 5.5% (3 of 55 subjects), and 10.3% (11 of 107 subjects), respectively. In hypertensive subjects, the incidences in the mirabegron dose groups were comparable to that in the placebo group. In addition, analysis on cardiovascular adverse events in Study CL-051 by concurrent hypertension showed that the incidences in non-hypertensive subjects at the maintenance dose of 50 mg and subjects at the increased dose of 100 mg were 13.7% (16 of 117 subjects) and 16.2% (6 of 37 subjects), respectively, while the incidences in hypertensive subjects at the maintenance dose of 50 mg and subjects at the increased dose of 100 mg were 17.1% (6 of 35 subjects) and 15.4% (2 of 13 subjects), respectively. The incidence was not largely different between subjects with and without concurrent hypertension. There were no events of which incidence was increased following the dose increase or long-term treatment in hypertensive subjects. To investigate effects of mirabegron on hypertensive subjects, blood pressure changes were examined in subgroups divided according to systolic blood pressure at the baseline (<140 mmHg or \geq 140 mmHg) and diastolic blood pressure at the baseline (<90 mmHg or \geq 90 mmHg). The results suggested that mirabegron dose not increase the blood pressure in subjects who were hypertensive at the baseline.

Of subjects with organic heart disorder, 1 subject each in the mirabegron 25 mg and 100 mg groups experienced cardiovascular adverse events. The event reported in the 25 mg group was mild and non-serious hypertension aggravated in a subject with angina pectoris, and it resolved during the mirabegron treatment period. The events in the 100 mg group were atrioventricular block first degree and conduction disorder in a subject with mitral regurgitation, mitral valve prolapsed, and angina pectoris, and it led to treatment discontinuation. The relationship to mirabegron cannot be ruled out for any event.

Mirabegron is demonstrated to have not only a potent agonistic effect on human β_3 -adrenoceptors but also agonistic effects on human β_1 - and β_2 -adrenoceptors, which are weak though. Therefore, cardiovascular effects possibly attributable to overdose of mirabegron were observed in safety pharmacology studies. However, in 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), the incidence of cardiovascular adverse events was as low as that in the placebo group. The occurrence of such events was a matter of concern due to the β -adrenoceptor agonistic effect, a pharmacological action of mirabegron. In Study CL-048, a difference in corrected mean changes in pulse rate from baseline to the final visit (dose group versus placebo group) in the mirabegron 50 mg group was 1.71 bpm on rising and 1.44 bpm at 6 hours post-dose, which were small and comparable to that in the tolterodine 4 mg group (0.77 bpm on rising, 2.88 bpm at 6 hours post-dose). As described above, effects of mirabegron were investigated in various patients at a cardiovascular risk in the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051) including elderly subjects, hypertensive subjects, and subjects with organic cardiac diseases. As a result, the incidence of adverse events in these subjects at a cardiovascular risk was comparable to that in subjects without such risk. In addition, no adverse events related to QTc prolongation were reported in any mirabegron group.

Based on the above, the applicant considers that the following statements in the package insert can sufficiently ensure the safety of mirabegron in patients at a cardiovascular risk: mirabegron should be administered with care in “patients with serious cardiac diseases” and “patients with long QT syndrome or patients on medication causing QT prolongation should be cautioned against overdosage.” in the “Important Precautions” section.

PMDA considers as follows:

The pharmacological action of mirabegron suggests cardiovascular effects. In non-clinical studies, deaths occurred in dogs and monkeys treated with mirabegron. In the safety pharmacology study in dogs, the heart rate increased was observed at below the clinical dose. The exposures at the NOAELs

in repeated-dose toxicity studies in rats, dogs, and monkeys were below the clinical exposure. In dogs, both dose and exposure were below the recommended clinical dose, and at doses below the clinical exposure, effects on ECG were observed.

In addition, mirabegron has been demonstrated to have agonistic effects on human β_1 - and β_2 -adrenoceptors, which are weak though. Clinical data suggest that an increase in heart rate is associated with mirabegron. Although the data from the Japanese clinical studies (Study CL-045, Study CL-048, Study CL-051) showed that the incidences of adverse events related to tachycardia or the other cardiovascular adverse events in the mirabegron dose groups were comparable to those in the placebo group, mirabegron was administered to only the limited number of patients with organic cardiac diseases in the clinical studies. Therefore, it cannot be ruled out that the conditions may be aggravated due to the increase in heart rate following administration of mirabegron to patients with underlying cardiac diseases such as angina pectoris and cardiac failure in clinical practice, if mirabegron is approved. As described above, Study CL-037, which served as the thorough QT/QTc study, suggested that mirabegron may cause QT prolongation. Furthermore, in consideration that mirabegron may be widely administered to elderly patients with concurrent diseases including cardiovascular ones continuously for an extended period, it is necessary to take more careful actions such as contraindications to the use of mirabegron in patients with serious cardiac diseases and listing catecholamines in “Precautions for concomitant use.” section. The details of cautions for mirabegron will be discussed at Expert Discussion.

4.(iii).B.(2).3) Patients with benign prostatic hyperplasia

The applicant explained the safety of mirabegron in patients with benign prostatic hyperplasia (BPH) as follows:

According to the Practice guidelines for Overactive Bladder (Guideline Committee for Overactive Bladder, The Japan Neurogenic Bladder Society, 2008), 50% to 75% of the elderly male BPH patients have OAB symptoms, and α_1 receptor antagonists are recommended as the first-line therapy for BPH patients with OAB symptoms. Although α_1 receptor antagonists alone resolve the OAB symptoms to some extent, the symptoms remain in some patients; the effects are not sufficient. Because by attenuating detrusor contraction, anticholinergics may cause dysuria aggravated or urinary retention in patients with BOO, the package inserts of anticholinergics include the following precaution in the Precautions for Indications section: “For patients with concurrent BOO diseases (BPH, etc.), treatment for these diseases (α_1 antagonists, etc.) should be prioritized.”

In the non-clinical pharmacology studies, mirabegron improved the bladder function at the doses not affecting the bladder contraction strength. In the urodynamic study (Study CL-060) in foreign male patients with lower urinary tract symptoms (LUTS) and BOO, no adverse effects on the maximum urinary flow rate or detrusor pressure at the maximum urinary flow rate were observed; mirabegron raised no safety issues and was well tolerated in patients. Furthermore, in the Japanese and foreign clinical studies conducted so far, mirabegron did not affect the residual urine volume, and adverse events such as urinary retention and dysuria were hardly reported. Based on the above, the applicant considers that mirabegron hardly affects urodynamics in patients with LUTS and BOO, and thus it is unlikely to aggravate the voiding function in those with BOO.

PMDA considers as follows:

From the urodynamic data, there has been no information available to justify a decision that administration of mirabegron should be restricted on all patients with BOO. However, taking into account that BOO were listed in the exclusion criteria for the Japanese clinical studies and treatment experience in these patients is limited, it is necessary to continue to pay attention to the safety information in these patients.

Concomitant use of mirabegron with α_1 receptor antagonists, which are frequently concomitantly

administered to BPH patients, are discussed in “4.(iii).B.(5).3) Concomitant use of α_1 receptor antagonists in patients with BPH.”

4.(iii).B.(2).4) Effects on eyes

After the filing of the application, glaucoma occurred in the foreign long-term treatment study (Study CL-049). The applicant informed PMDA that in response to this event, the FDA requested them to evaluate effects on eyes by conducting a study. PMDA asked the applicant to explain ocular adverse events reported in the clinical studies, applicant's view on the safety on eyes, and contents of the discussion with the FDA.

The applicant explained as follows:

Major factors affecting the intraocular pressure include ciliary production of aqueous humor, its movement into the anterior chamber, and its drainage from the anterior chamber. Although the production of aqueous humor is enhanced by a β_2 receptor agonistic effect, mirabegron does not exert the β_2 receptor agonistic effect at around the clinical dose. Therefore, mirabegron is unlikely to enhance the production of aqueous humor and to increase the intraocular pressure. Although the drainage of aqueous humor is enhanced by β receptor agonistic effect, which subtype of the β receptor is involved remains unknown. However, even if β_3 receptor is involved, mirabegron enhances the drainage of aqueous humor, only decreasing the intraocular pressure. Movement of aqueous humor is interfered by relaxation of the iris sphincter or contraction of the pupillary dilator. The iris sphincter is governed by the parasympathetic nerve and relaxed by M_3 receptor antagonism. The pupillary dilator is governed by the sympathetic nerve and contracts in response to an α_1 receptor agonistic effect. Therefore, mirabegron is unlikely to be involved in the movement of aqueous humor. In addition, in the 26-week repeated dose study in rats and 52-week repeated dose study in cynomolgus monkeys, ophthalmological and histopathological examination did not show any change related to mirabegron.

In the phase I single and multiple dose study (Study CL-034), visual acuity test and funduscopy were performed to investigate effects of mirabegron on eyes. As a result, neither clinically significant visual acuity changes nor abnormal findings in the fundus were noted in any subject. Of adverse events reported in the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), those classified into Eye disorders (MedDRA/J Version 12.1 SOC) were extracted from the combined data of Study CL-045 and Study CL-048 for analysis. As a result, the incidence of adverse events in Eye disorders in the placebo group, the mirabegron 25 mg group, the mirabegron 50 mg group, and the mirabegron 100 mg group was 0.7%, 1.4%, 1.7%, and 1.0%, respectively. The incidences in the mirabegron dose groups were slightly higher than that in the placebo group, but the incidence did not show any dose-dependent increasing trend. The incidence of individual events in the mirabegron dose groups was comparable to those in the placebo group. No glaucoma occurred. In Study CL-051, the incidence of adverse events in Eye disorders was 5.3% in subjects at the maintenance dose of 50 mg and 10.0% in subjects at the increased dose of 100 mg. The events reported by ≥ 2 subjects in each group were only asthenopia in 3 subjects at the maintenance dose of 50 mg and blepharitis in 2 subjects at the increased dose of 100 mg, and the other events occurred only in 1 subject. All events are mild in severity, and the severity was not aggravated by the long-term treatment. No glaucoma occurred. In the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), glaucoma was not aggravated in subjects with concurrent glaucoma (6 subjects, 2 subjects, and 2 subjects, respectively) following administration of mirabegron. Based on the above, the applicant considers that mirabegron is unlikely to have safety issues on eyes in clinical use.

The applicant reported the cases of glaucoma in 2 subjects in the foreign long-term treatment study (Study CL-049) to the FDA in accordance with the SAE reporting procedure. The FDA requested the applicant to report additional information about the 2 subjects as well as tabulation results of all events of glaucoma including SAE in all clinical studies of mirabegron (including

Japanese studies) to the FDA. Adverse events under a category of “glaucoma” were extracted according to SMQ. As a result, glaucoma or adverse events suspected of glaucoma were observed in a total of 12 subjects including 2 with the above SAE (11 subjects treated with mirabegron and 1 subject treated with tolterodine, all in foreign studies). The applicant followed up the ophthalmic medical records of the 12 subjects and examined them with external ophthalmologists. As a result, 3 subjects were definitely judged to have experienced glaucoma or aggravation of pre-existing glaucoma during the study period (2 subjects treated with mirabegron, 1 subject treated with tolterodine). In addition, 2 subjects, in which the possibility that glaucoma may have occurred or have been aggravated during the study period (both treated with mirabegron) cannot be ruled out, were found. In the remaining 7 subjects, glaucoma was not identified as adverse events. In 4 subjects with glaucoma or probable glaucoma, the incidence was analyzed by treatment period. As a result, the incidence was 0.04% (2 of 4759 subjects) during the period of 4 to 12 weeks (phase II and phase III studies) and 0.11% (2 of 1835 subjects) during the period of 12 months (long-term treatment study), which were lower than 0.12% to 0.24%, the background incidence of glaucoma. Furthermore, intraocular pressure data obtained from the multiple dose study on gender-related difference and in elderly (Study CL-031) and phase I single and multiple dose study (Study CL-034) were analyzed, resulting in absence of notable findings. Literature search was performed for reports on distribution of β_3 -adrenoceptors in intraocular tissues and functions involved in the production and drainage of aqueous humor. Based on the above information, analysis results, and results of the literature search, the applicant reported to the FDA that mirabegron is unlikely to increase the intraocular pressure.

The FDA presented the following views: It is difficult to determine whether glaucoma or adverse events suspected of glaucoma in the mirabegron dose groups may have been accidental or induced by mirabegron, and it is necessary to conduct a clinical study using the intraocular pressure as an endpoint in order to verify non-inferiority of mirabegron to placebo. The applicant submitted the protocol of a placebo-controlled, randomized, double-blind, parallel-group study, which was conducted as a clinical pharmacology study on intraocular pressure to verify non-inferiority (non-inferiority margin, 1.5 mmHg) of mirabegron at the dose of 100 mg to the placebo in terms of changes in intraocular pressure following administration of these study drugs to subjects with normal intraocular pressure including OAB patients for 8 weeks (target sample size, 240 subjects [120 subjects per group]). The protocol is currently under review at the FDA. On agreement with the FDA, the study will be started immediately. The study data will be available by ■ to ■ 20■.

PMDA considers as follows:

The applicant has claimed that mirabegron does not have a high risk of causing glaucoma, by presenting the following findings: (i) the β_2 -adrenoceptor agonistic effect of mirabegron is weak and thus unlikely to enhance production of aqueous humor or to reduce drainage of aqueous humor and (ii) the incidence of glaucoma in the clinical studies is low and comparable to the background incidence of glaucoma. However, the protocols of many clinical studies did not specify ophthalmological examination. Therefore, diagnosis of glaucoma was made only in cases where subjects had subjective symptoms or had an opportunity to see an ophthalmologist, and the other subjects had no chance to undergo ophthalmological examination. Accordingly, a mild increase in intraocular pressure may not be detected as an adverse event in clinical studies. At present, information about changes in the intraocular pressure before and after administration of mirabegron is insufficient and it is careless for the applicant to judge that mirabegron does not increase the intraocular pressure in humans. In consideration that mirabegron may be administered for an extended period, it is important to collect quantitative data about the intraocular pressure. At present, it is necessary not only to list patients with glaucoma under “Careful Administration” section in the package insert but also to include a caution stating that attention should be paid to the safety of eyes. For instance, patients should see an ophthalmologist periodically while taking mirabegron.

4.(iii).B.(2).5) Tumorigenesis

After the filing of the application, a difference in the incidences of tumors were found among the dose groups in the foreign long-term treatment study (Study CL-049). The applicant informed PMDA that they reported the finding at the meeting with the FDA on ■■■, 20■■■.

PMDA asked the applicant to explain their views on effects of mirabegron on tumorigenesis and details of the meeting with the FDA.

The applicant explained as follows:

Non-clinical studies did not present any finding suggesting genotoxicity or carcinogenicity of mirabegron.

In the Japanese long-term treatment study (Study CL-051), ovarian neoplasm and basal cell carcinoma were found in 1 each of the subjects at the maintenance dose of 50 mg and the subjects at the increased dose of 100 mg, respectively. The incidence of tumors in the study overall was 1.0%.

The incidence of tumors (classified into Neoplasms benign, malignant and unspecified [incl cysts and polyps] under MedDRA/J Version 12.1 SOC) in the foreign long-term treatment study (Study CL-049) was 0.9% (7 of 812 subjects) in the mirabegron 50 mg group, 1.8% (15 of 820 subjects) in the mirabegron 100 mg group, and 1.0% (8 of 812 subjects) in the tolterodine group. The types of tumors reported in the mirabegron 100 mg group did not show any specific trend, and the incidence of tumors did not tend to increase with long-term treatment. Therefore, the causal relationship to mirabegron was unlikely.

As described above, in the Japanese and foreign phase II and phase III studies (Study CL-045, Study CL-048, Study CL-044, Study CL-046, Study CL-047), the incidence of tumors in any mirabegron dose group was comparable to that in the placebo group or tolterodine group. Therefore, mirabegron is very unlikely to cause tumors. In addition, the FDA was concerned about the difference in the incidences of tumors among dose groups, but so far the applicant has not received any directions about more specific actions (additional non-clinical data, etc.).

PMDA considers as follows:

Given that currently available data do not show definite effects of mirabegron on the incidence of malignant tumors, and that mirabegron has only been administered for up to 52 weeks so far, the risk associated with the longer-term treatment remains unknown. Therefore, it is necessary to continue to collect relevant information, such as research reports published in Japan and overseas, even after marketing.

PMDA considers as follows:

Currently available clinical data ensure the tolerability of mirabegron at the dose of 50 mg in Japanese patients with OAB. However, the pharmacological action of mirabegron generates a concern about a cardiovascular risk, and actually cardiovascular adverse events such as arrhythmia were frequently observed in non-clinical studies with some deaths in dogs and monkeys. Therefore, the cardiovascular risk of mirabegron cannot be ruled out. Clinical studies also suggested not only the risk of QT prolongation but also potential risks of glaucoma and malignant tumors, and these risks cannot be ruled out by the currently available information. In addition, mirabegron is expected to be mainly administered to elderly patients, who often have concurrent diseases and may receive various concomitant medications. However, clinical studies have not thoroughly covered such diverse medical conditions. Taking into account that mirabegron involves a new mechanism of action and the currently available information is limited, it is important to provide cautions more specifically in the package insert in terms of the

characteristics of patients in whom mirabegron is contraindicated or the precautions for the mirabegron treatment, so far as information is available. Furthermore, it is necessary to continue to collect extensive safety information, and post-marketing pharmacovigilance is critically important. It is essential to take safety measures immediately whenever new information becomes available from the additional foreign thorough QT/QTc study, currently ongoing foreign clinical study for glaucoma, and post-marketing surveillance. At the same time, it is important to review the risk-benefit balance in consideration of the patient characteristics (including medical conditions).

4.(iii).B.(3) Clinical positioning

PMDA asked the applicant to explain the clinical positioning of mirabegron compared with existing therapeutic drugs for OAB.

The applicant explained as follows:

At present, the treatment of OAB mainly involves pharmacotherapy. Drugs that are widely used currently are muscarinic antagonists such as solifenacin succinate, tolterodine tartrate, imidafenacin, and propiverine hydrochloride. The muscarine receptor is expressed in not only the bladder but also salivary gland, intestinal tract, and ciliary muscle, playing functional roles. Such muscarinic antagonists may cause adverse drug reactions such as dry mouth, constipation, and vision blurred. In addition, because muscarinic antagonists suppress bladder contraction, adverse drug reactions such as dysuria, increased residual urine volume, and urinary retention are matters of concern. It has been reported that approximately 25% of patients taking muscarinic antagonists discontinued the medication due to adverse drug reactions (*Drugs Aging*. 1995;6:243-62, *Japanese journal of urological surgery*. 2009;22:1493-7). Therefore, development of therapeutic drugs for OAB that have effects comparable or superior to the existing drugs and that reduce the risk of adverse drug reactions related to muscarinic antagonists has been desired (*Japanese journal of urological surgery*. 2009;22:1487-92). Mirabegron is a selective β_3 -adrenoceptor agonist with a new mechanism of action, which is different from that of the existing drugs, potentially reducing adverse drug reactions, compared with muscarinic antagonists and is thus expected to become a new therapeutic drug for OAB. The development has thus proceeded.

In Study CL-048 in which tolterodine at the dose of 4 mg, a globally recognized standard drug for treatment of OAB, was used as a comparator, the mirabegron 50 mg group showed superiority to the placebo group in all endpoints for the symptoms including mean number of micturitions, mean number of urgency episodes, and mean number of urinary incontinence episodes, and data in the mirabegron 50 mg group were numerically superior to those in the tolterodine 4 mg group, although statistical analysis was not performed. As described above, the efficacy of mirabegron is comparable or superior to that of the existing therapeutic drugs, which is considered to be an advantage.

Regarding safety, there was no difference in the incidence of adverse events (including abnormal changes in laboratory test values) between the placebo and mirabegron 50 mg groups in Study CL-048, and the incidence in the mirabegron 50 mg group was found to be the lowest among the dose groups. Muscarinic antagonists may cause dry mouth, constipation, vision blurred, and dysuria through their anticholinergic effects, raising clinical problems, which have interfered with the drug compliance (*Japanese journal of urological surgery*. 1996;9:373-7, *Voiding Disorders Digest*. 2000;8:3-38). However, the incidence of dry mouth in the mirabegron 50 mg group is comparable to that in the placebo group and lower than that in the tolterodine 4 mg group. The incidences of constipation, vision blurred, and dysuria in the mirabegron dose groups were lower than those in the tolterodine 4 mg group and comparable to those in the placebo group. Non-clinical pharmacology studies have showed that mirabegron reduces bladder contraction frequency without affecting the bladder contraction strength. In the urodynamic study (Study CL-060), mirabegron was administered once daily to foreign male patients with LUTS and BOO at

the dose of 50 mg or 100 mg for 12 weeks, but the maximum urinary flow rate or the detrusor pressure at the maximum urinary flow rate was not affected. Furthermore, in the clinical studies conducted so far, mirabegron did not affect the residual urine volume, and there were little adverse events such as dysuria and urinary retention. In the 3 Japanese studies (Study CL-045, Study CL-048, and Study CL-051), cardiovascular adverse events, which were matters of concern due to the β -adrenoceptor agonistic effect, a pharmacological action of mirabegron, were analyzed. As a result, the incidences of adverse events related to tachycardia (tachycardia, palpitations, heart rate increased) and of the other cardiovascular adverse events (adverse events classified into Cardiac disorders, Investigations, and Vascular disorders) in the mirabegron dose groups were comparable to those in the placebo group. Effects of mirabegron on pulse rate are small, and its QTc prolongation effect is also unlikely to cause clinical concern.

As described above, mirabegron has the efficacy comparable or superior to that of muscarinic antagonists currently widely used at present, and for the safety, it is positioned as a therapeutic drug for OAB that can alleviate adverse drug reactions such as dry mouth, constipation, vision blurred, and dysuria, which have been recognized as problems related to the existing therapeutic drugs. Accordingly, the applicant recognizes that mirabegron can be expected as a new therapeutic drug that can replace the existing therapeutic drugs and has a potential to be the first-choice medication for OAB.

PMDA considers as follows:

The efficacy of mirabegron at the dose of 50 mg in patients with OAB has been demonstrated. The data from Study CL-048, which compared mirabegron with the existing drug, tolterodine, did not suggest that the efficacy of mirabegron at the dose of 50 mg was largely different from that of tolterodine at the dose of 4 mg. In addition, the applicant claimed that it would be an advantage that the efficacy of mirabegron was comparable or superior to that of the existing therapeutic drugs. However, Study CL-048 did not statistically compare mirabegron at the dose of 50 mg with tolterodine at the dose of 4 mg. It is inappropriate that the applicant determined that the efficacy of mirabegron was comparable or superior to that of the existing drugs.

Based on the efficacy data of mirabegron at the dose of 50 mg and in consideration that the mirabegron treatment were well tolerated in the clinical studies, mirabegron can be a treatment option for OAB. On the other hand, mirabegron is a therapeutic drug for OAB with a new mechanism of action and the currently available information on the clinical use of mirabegron is limited both in Japan and overseas. As previously described in the “Safety” section, the non-clinical and clinical studies suggested multiple risks involving fatal diseases. In consideration that mirabegron will be used to improve the QOL, patients who may experience serious, fatal or irreversible adverse events following administration of mirabegron should avoid taking the drug. Therefore, the use of mirabegron should be considered before initiating the therapy, based on the benefit and risk involved in administration of mirabegron, and after the prescription. In addition, the necessity of extended treatment should be periodically determined in consideration of the adverse events and concurrent diseases. It is also highly important to continue to collect safety information from both clinical and non-clinical experiences.

Based on the above, PMDA considers that mirabegron can be a treatment option for OAB, but mirabegron is not a drug positioned as the first-line medication for OAB with precedence over anticholinergics at present, because (a) the currently available information has not clearly demonstrated the superiority of mirabegron to the existing anticholinergics in terms of the efficacy, (b) while extensive clinical use of anticholinergics has provided adequate volume of the safety information, the clinical use of mirabegron is limited, although it was well tolerated in subjects in the clinical studies, and (c) the non-clinical studies showed various toxicological findings, generating concerns about multiple potential risks. The applicant claims that mirabegron is unlikely to cause urinary retention and can be used safely even in patients with LUTS and BOO.

However, information about the efficacy and safety in these patients is limited and not sufficient to draw a judgment that the usefulness can be expected, because the urodynamic study did not thoroughly evaluate the efficacy and safety of mirabegron in these OAB patients and the major clinical studies evaluating the efficacy and safety of mirabegron scarcely included patients with LUTS and BOO.

4.(iii).B.(4) Indications

PMDA considers it appropriate to set the indications of mirabegron as “Urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder” as proposed by the applicant, taking into account that Study CL-048, the Japanese phase III study, has demonstrated the efficacy of mirabegron at the dose of 50 mg in terms of any of mean number of micturitions, number of urgency episodes, and number of urge urinary incontinence episodes.

4.(iii).B.(5) Dosage and administration

4.(iii).B.(5).1 Dosage

The proposed dosage and administration was “The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal. The dose may be adjusted according to the patient’s age and symptoms, and the maximum daily dose is 100 mg.”

The Japanese phase II study (Study CL-045) demonstrated the efficacy of mirabegron at any study dose (25 mg, 50 mg, 100 mg) in terms of the mean number of micturitions, the primary endpoint, as well as mean number of urinary incontinence episodes and mean number of urge urinary incontinence episodes, the secondary endpoints, compared with the placebo. Then, in the Japanese phase III comparative study (Study CL-048), mirabegron was investigated at the dose of 50 mg.

The applicant explained the reason why 50 mg was selected as follows:

By PPK analysis of Study CL-045, the mean plasma concentration at steady state (C_{ss}) was estimated for each subject to investigate the relationship with the efficacy endpoint. As a result, the effect of the change in mean number of micturitions, the primary endpoint, did not reach the peak at around C_{ss} in the 25 mg group, and the maximum effect was observed at around C_{ss} in the 50 mg group, suggesting that mirabegron at the dose of 50 mg exerts an effect which is adequate and comparable or superior to that of the existing drugs.

The Japanese long-term treatment study (Study CL-051) was conducted after completion of Study CL-045 and before Study CL-048. In this study, the treatment with mirabegron was initiated at the dose of 50 mg, but the protocol allowed the dose to be increased from 50 mg to 100 mg only when the investigator judged that the drug effect was insufficient at the visit at Week 8 and when the subject had no safety issues and requested the dose increase. When Study CL-048 was being planned, not all of the subjects in Study CL-051 were assessed for dose increase at Week 8, but subjects treated with the increased dose of mirabegron accounted for 20% to 30% of the subjects enrolled, from which it was inferred that the percentage of the subjects on the increased dose remains unchanged throughout the study. Therefore, the applicant determined that the main clinical dose of mirabegron was 50 mg, and the increased dose of 100 mg was positioned as an optional.

Based on the above, the objective of Study CL-048 was to clarify the clinical positioning of mirabegron by comparing the efficacy and safety at the prospective main dose of 50 mg with placebo or tolterodine at the dose of 4 mg. Since the data from Study CL-045 demonstrated that the efficacy of mirabegron at the dose of 100 mg was comparable or superior to that at the dose of 50 mg, and the applicant considered that the safety could be evaluated based on the data from Studies CL-045 and CL-051 as well as the foreign phase III studies (Study CL-046, Study CL-047). For this reason, the dose of 100 mg was not set in Study CL-048.

In addition, the data from Study CL-048 confirmed the efficacy of mirabegron at the dose of 50 mg, and the safety was determined to be allowable. Based on the above, the applicant considered that the dose of mirabegron 50 mg was appropriate as the recommended clinical dose.

PMDA considers as follows:

Concerning the dose selection for the mirabegron group in Study CL-048, the applicant has not thoroughly explained the reason why they did not select 25 mg/day, but, it is acceptable to select 50 mg based on the data from Study CL-045 and foreign clinical data, and Study CL-048 re-confirmed the efficacy and safety of mirabegron at the dose of 50 mg, thus the recommended clinical dose of 50 mg/day is appropriate for mirabegron.

PMDA asked the applicant the reason for selection of the maximum daily dose at 100 mg in the proposed dosage and administration, allowing the dose increase.

The applicant explained as follows:

Study CL-045 demonstrated the superiority of mirabegron at any dose to the placebo in terms of change in mean number of micturitions per 24 hours as the primary endpoint, as well as change in mean number of urinary incontinence episodes per 24 hours and change in mean number of urge urinary incontinence episodes per 24 hours as the secondary endpoints. Although the dose response was not clear in any endpoint, ANCOVA using the baseline as a covariate showed the dose-dependent improvement. In addition, change in mean number of urgency episodes per 24 hours increased with increasing dose, and there was a statistically significant difference only between the mirabegron 100 mg group and placebo group. Change in the mean voiding volume per session (mean voiding volume) increased with increasing dose, and a statistically significant difference was found in all of the mirabegron dose groups compared with the placebo group. As described above, data of the mean number of urgency episodes and mean voiding volume at the mirabegron dose of 100 mg were numerically superior to those at the dose of 50 mg, and thus the efficacy at the dose of 100 mg was comparable or superior to that at the dose of 50 mg. In Study CL-051, the dose was increased to 100 mg in subjects who had not sufficiently responded to mirabegron at the dose of 50 mg, although the number was limited. In these subjects at the increased dose of 100 mg, further improving trends were noted in all voiding parameters including not only the mean number of micturitions but also mean number of urgency episodes and mean number of urinary incontinence episodes, and the efficacy remained stable until Week 52, as noted in subjects at the maintenance dose of 50 mg.

Regarding safety, a dose-response relationship was observed for the incidence of adverse events (including abnormal changes in laboratory test values) during the treatment period in Study CL-045, but, a significant dose-response relationship was not observed for the incidence of adverse events of which a causal relationship to the study drug could not be ruled out (adverse drug reactions) and any dose-responsive relationship was not found in the cardiovascular effects including effects on pulse rate and QT/QTc interval. Therefore, the applicant considered that the dose increase to 100 mg raises no safety concerns. Study CL-051 was designed to use an optional titration method, but no considerable differences were observed in the occurrence of adverse events between subjects at the maintenance dose of 50 mg and subjects at the increased dose of 100 mg, and thus mirabegron at the dose of 100 mg was free from the safety issues and was well tolerated.

Based on the above, the applicant considered it useful to increase the dose to 100 mg for patients who do not respond to the 50-mg dose sufficiently, and thus the above dosage and administration were proposed.

PMDA considers as follows:

It is not appropriate to set 100 mg as an optional increased dose because the clinical significance

of the dose increase of mirabegron to 100 mg has not been demonstrated, and effects of the increased dose remain unclear while the risks associated with the dose increase may increase. This decision is based on the following reasons:

- The data from Study CL-045 showed that the efficacy of mirabegron at the dose of 100 mg was not superior to that at the dose of 50 mg in terms of the primary endpoint and multiple secondary endpoints.
- Study CL-051 was designed as an open-label uncontrolled study, which would not allow evaluation of the effects separately from the placebo effect associated with the dose increase. It is difficult to strictly evaluate the effects of the increased dose of 100 mg.
- The exposure of mirabegron was increased in a dose proportional manner when the dose was increased from 50 mg to 100 mg. The risk including QT prolonged may be increased.

In consideration of the above, PMDA asked the applicant to re-examine the appropriateness of the dose increase to 100 mg.

The applicant explained as follows:

The clinical data both in Japan and overseas were comprehensively interpreted again. As a result, (i) the efficacy of mirabegron was considered to reach almost the peak at the dose of 50 mg, (ii) it is difficult to strictly evaluate only the effects of the increased dose of 100 mg using the data from Study CL-051, (iii) it is difficult to predefine and classify the patient population in which mirabegron at the dose of 100 mg is useful and needed, and (iv) using the currently available data, the clinical significance of the increased dose of 100 mg cannot be clearly presented. Therefore, the maximum clinical dose of mirabegron at 50 mg was selected and the dosage and administration was changed to “The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal.”

PMDA has concluded that the changed dosage and administration in which the clinical dose and maximum dose of mirabegron are set at 50 mg is appropriate.

4.(iii).B.(5).2) Concomitant use of mirabegron with anticholinergics

In consideration that anticholinergics are widely used for treatment of OAB at present, PMDA considers that mirabegron with a different mechanism of action from that of anticholinergics may be used concomitantly with them in OAB patients who have not sufficiently responded to the previous medication after mirabegron becomes available for use in clinical practice. PMDA asked the applicant to explain the efficacy and safety of concomitant use of anticholinergics with mirabegron as well as their views on whether or not such concomitant use is recommended.

The applicant explained as follows:

Mirabegron is expected to be a new therapeutic drug for OAB that has the efficacy comparable or superior to that of the existing therapeutic drugs and the adequate safety, it will be used alone as a first-line drug for OAB patients or replace the preceding anticholinergics in patients who have not sufficiently responded to the previous medication. In any case, mirabegron is predicted to be used alone basically, and thus no clinical studies were conducted to evaluate the safety and efficacy of concomitant use of anticholinergics with mirabegron before the filing of the application. Therefore, clinical data on the safety and efficacy of the concomitant use are not available, and thus a caution will be provided by stating in the “Important Precautions” section in the package insert that it is desirable to avoid the concomitant use of these drugs.

However, the current pharmacotherapy for OAB mainly consists of anticholinergics, but sufficient therapeutic effects cannot be achieved by the anticholinergics alone in some patients. On the other hand, mirabegron alone may not provide sufficient effects in some patients. Therefore, a possibility of concomitant use of mirabegron with anticholinergics in clinical practice

cannot be ruled out for patients who have not sufficiently responded to either drug, and the prohibition of such concomitant use may reduce therapeutic options. Therefore, the conduct of a clinical study in OAB patients outside of Japan is under consideration to investigate the safety and efficacy of concomitant use of mirabegron with solifenacin. The applicant will revise the description once the resultant study data confirm the safety of the concomitant use and indicate that the benefit of such use outweighs the risk.

Mirabegron has a moderate CYP2D6 inhibitory effect. Of anticholinergics indicated for OAB in Japan, only tolterodine is mainly metabolized by CYP2D6. Concomitant use of mirabegron with tolterodine may increase the tolterodine concentration and decrease the DD01 concentration by inhibition of CYP2D6, but the sum of AUC values of these non-binding forms may not be largely changed. From the viewpoint of pharmacokinetics, the efficacy and safety of the concomitant use will have no particular problems. Of anticholinergics other than tolterodine, solifenacin was used concomitantly with mirabegron in both non-clinical and clinical studies. In the 13-week concomitant oral repeated-dose toxicity study of solifenacin and mirabegron in mice, the concomitant administration of these drugs did neither increase the toxicity nor cause another toxicity.

PMDA considers as follows:

Since the applicant could have assumed even at the development stage that mirabegron may be used concomitantly with an existing therapeutic drug for OAB with a different mechanism of action in patients who have not sufficiently responded to mirabegron or anticholinergics, the applicant should have investigated the efficacy and safety of concomitant use before regulatory submission, by conducting drug-drug interaction studies with anticholinergics and clinical studies for the safety of concomitant use of mirabegron with anticholinergics in Japanese OAB patients. In addition, even though until the application, the applicant considered that it would be desirable to avoid concomitant use of mirabegron with anticholinergics, after that the applicant explained the safety of concomitant use of mirabegron with tolterodine or solifenacin based on non-clinical data and speculation from a viewpoint of pharmacokinetics. However, PMDA does not consider that merely the discussion based on indirect speculation can ensure the safety and efficacy of the concomitant use. The currently available information on the concomitant use is extremely limited. PMDA has concluded that it is appropriate to advise that concomitant use of mirabegron with anticholinergics should be avoided. The details of appropriate precautions against the concomitant use of anticholinergics with mirabegron will be discussed at the Expert Discussion and be further reviewed.

4.(iii).B.(5).3) Concomitant use of mirabegron with α_1 receptor antagonists in patients with BPH

PMDA asked the applicant to explain the safety of mirabegron, in OAB patients with BPH, used concomitantly with α_1 receptor antagonists which are widely used in BPH patients.

The applicant explained as follows:

The 2 foreign phase III studies (Study CL-046, Study CL-047) included patients with concurrent BPH, and the use of α_1 receptor antagonists was also allowed. Subgroup analysis in patients with concurrent BPH was performed to compare the incidence of adverse events with and without concomitant use of α_1 receptor antagonists. In either study, the adverse events and incidence were not largely different between with and without concomitant use of α_1 receptor antagonists. Such concomitant use were unlikely to affect the safety profile. Although urinary retention and orthostatic hypotension are matters of concern in association with anticholinergics and α_1 receptor antagonists, respectively, no differences were observed in the occurrence of such events between with and without their concomitant use. Since the number of subjects included in this subgroup analysis were limited, in terms of the efficacy, any consistent trend was not observed between subjects treated concomitantly with mirabegron and α_1 receptor antagonists and those treated with

mirabegron alone. Concerning pharmacokinetic interactions between mirabegron and α_1 receptor antagonists, it has been reported that concomitant use of tamsulosin with paroxetine, which may be a more potent CYP2D6 inhibitor than mirabegron, resulted in 1.3- and 1.6-fold increases in C_{max} and AUC of tamsulosin, respectively. In consideration of the potency of CYP2D6 inhibitory effect of mirabegron, the effect of mirabegron on pharmacokinetics of tamsulosin would be smaller than that of paroxetine. Of α_1 receptor antagonists used in BPH patients other than tamsulosin, only urapidil has a statement on involvement of CYP2D6 in its metabolism in the package insert, and a possibility that concomitant use of urapidil with mirabegron increases the plasma urapidil concentration cannot be ruled out. However, the concomitant use of urapidil with mirabegron is unlikely to cause significant issues because urapidil has not had a caution for concomitant use with potential CYP2D6 inhibitors. Therefore, concomitant use of α_1 receptor antagonists with mirabegron is unlikely to cause significant issues in terms of the pharmacokinetic interactions. Mirabegron has a low risk of aggravation of symptoms such as urinary retention and dysuria, and the applicant thus considers it possible to start the treatment with mirabegron in BPH patients with OAB symptoms concomitantly with α_1 receptor antagonists.

Taking into account that experience of concomitant use of mirabegron with α_1 receptor antagonists is limited, PMDA considers it necessary to continue to pay attention to the safety of such concomitant use.

4.(iii).B.(6) Quality of clinical studies

Although Study CL-048 was designed as a study including 12 weeks of treatment, subjects who took the double-blind study drug for “ ≥ 10 weeks and < 12 weeks” accounted for 72.6% (267 of 368 subjects) in the placebo group, 72.4% (267 of 369 subjects) in the mirabegron 50 mg group, and 69.8% (257 of 368 subjects) in the tolterodine 4 mg group. Although the period falls within the allowable range with respect to the standard day for observation and examination in consideration of the subjects’ convenience for visits (allowance; the allowance for efficacy analysis at Week 12 of the treatment period ranged from Day 70 to Day 97 [standard day, Day 84]), these subjects completed the study before Week 12. PMDA asked the applicant to explain the effect of the early completion. The applicant submitted analysis data from Study CL-048 on the subgroups classified according to the treatment period, which did not show any different trend between the subgroups in terms of the subject demographics and data on the efficacy and safety, and replied that the difference of the treatment period within the allowance was unlikely to affect evaluation of the efficacy and safety. In consideration that visit days of these subjects fell within the allowance specified in the protocol, and no considerable difference was observed in subject demographics or data on the efficacy and safety between subgroups divided according to the treatment period within this range, PMDA considered that it is possible to evaluate mirabegron using the data from Study CL-048, and evaluated the efficacy and safety.

4.(iii).B.(7) Post-marketing surveillance etc.

The applicant explained the post-marketing surveillance plan as follows:

In accordance with “Pharmacovigilance Planning” (PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001 dated September 16, 2005; hereinafter referred to as “ICH E2E”), the applicant examined the contents to be monitored after marketing of mirabegron. As a result, the applicant planned a use-results survey (observation period, 12 weeks; surveillance period, 3 years) in 10,000 patients and a long-term specified use-results survey (observation period, up to 2 years; surveillance period, 3 years) in 300 patients. As the primary surveillance items for use-results survey, the safety and efficacy in patients with hepatic impairment and patients with renal impairment, the safety and efficacy of mirabegron administered concomitantly with the other drugs, and the safety and efficacy of the concomitant drugs will be selected.

In accordance with ICH E2E, important potential risks of mirabegron include QT prolongation, glaucoma, effect on heart rate, patients with hepatic impairment, and patients with renal

impairment. The effect on heart rate and treatment consequences in patients with hepatic impairment and patients with renal impairment will be investigated in the use-results survey and specified use-results survey, but for QT prolongation and glaucoma, the safety will be evaluated using the data from the clinical studies conducted based on the discussion with the FDA. The important missing information include limited patients on the treatment for an extended period of ≥ 1 year, lack of the treatment experience in patients with severely hypertension (excluded from the clinical studies according to the exclusion criteria), lack of the treatment experience with anticholinergics both in Japan and overseas, lack of the treatment experience with concomitant α_1 receptor antagonists in Japan, limited treatment experience at the dose of 25 mg/day in the clinical studies, and limited treatment experience in elderly OAB patients, who are considered to account for a large percentage of the users after marketing because OAB develops mostly in the elderly. The relevant information will be collected from the use-results survey and subjected to subgroup analysis by patient demographics for evaluation of the safety and efficacy. In addition, there is no treatment experience in children or pregnant, nursing, or lactating women, who were excluded from the clinical studies according to the exclusion criteria. A course of these users in the use-results survey will be evaluated and the effects of the use in pregnant and nursing women on delivery and neonates will be followed up.

PMDA considers as follows:

In consideration that mirabegron is a drug with a new mechanism of action and that the experience of use of the drug in Japan and overseas is limited, collection of the safety information based on the actual use in clinical practice is important, and it is appropriate to conduct not only the use-results survey but also specified use-results survey for the long-term safety. It is necessary to investigate the clinical course in patients with hypertension and the elderly and effects of concomitant drugs, while details of such investigations should be further examined. Concerning QT prolongation and glaucoma, the applicant explained that the information will be obtained from the clinical studies conducted based on the discussion with the FDA. However, it is a problem not to include these matters in the survey plan in Japanese patients although the risks of those events have not been ruled out so far. Therefore, it is necessary to collect information about adverse events related to QT prolongation and TdP. A final decision on post-marketing considerations will be made, taking account of comments in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

Described in Review Report (2).

IV. Overall Evaluation

As a result of the review described above, PMDA determined that the efficacy of mirabegron in patients with OAB has been demonstrated based on the submitted data. Concerning whether or not the safety is acceptable in view of its observed benefits, PMDA cannot underestimate the fact that various toxicological findings such as cardiovascular risk and effects on eyes and reproductive organs, which may not have been sufficiently investigated in clinical studies, have been observed in non-clinical studies, although clearly unacceptable risks have not been observed in clinical studies. Therefore, it is necessary to take measures such as advising cautions to ensure the safety of patients treated with mirabegron and providing related information. In addition, it is necessary to consider what cautions are appropriate for concomitant use of mirabegron with anticholinergics, approved therapeutic drugs for OAB, as well as that of mirabegron with α_1 receptor antagonists in BPH patients. In consideration of the above, details of cautions and information to ensure proper use of mirabegron as well as appropriate contents of the post-marketing surveillance will be discussed at the Expert Discussion. PMDA considers that mirabegron may be approved if it can be concluded based on comments from the Expert

Discussion that there are no particular problems.

Review Report (2)

May 12, 2011

I. Product Submitted for Registration

[Brand name]	Betanis Tablets 25 mg Betanis Tablets 50 mg
[Non-proprietary name]	Mirabegron
[Applicant]	Astellas Pharma Inc.
[Date of application]	June 18, 2010

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

The Japanese phase II study (Study CL-045) and Japanese phase III study (Study CL-048) were designed to investigate the efficacy of mirabegron compared with the placebo. The following conclusions of PMDA on these studies have been supported by the expert advisors: (a) the efficacy of mirabegron at the dose of 50 mg has been demonstrated, (b) it is acceptable to omit verification of non-inferiority of mirabegron to tolterodine in the confirmatory study, and (c) the efficacy of mirabegron at the dose of 50 mg will not be attenuated following the long-term treatment, since the improved conditions were constantly maintained until Week 52 (the final visit) in the Japanese long-term treatment study (Study CL-051). [For the dosage and administration, see “(6) Dosage and administration.”]

(2) Safety

Based on the data from the Japanese phase II study (Study CL-045), Japanese phase III study (Study CL-048), and Japanese long-term treatment study (Study CL-051), PMDA has concluded that the tolerability of mirabegron has been demonstrated and there were no specific adverse events associated with long-term treatment. The conclusion of PMDA has been supported by the expert advisors. On the other hand, since treatment experience with mirabegron with a new mechanism of action in OAB patients is limited, PMDA has concluded that it is necessary to continuously pay attention to multiple risks suggested by non-clinical data. The expert advisors have also supported the PMDA’s conclusion. In addition, the following issues were discussed.

(2).1) Cardiovascular risk

a. Risks of QT/QTc prolongation and arrhythmogenesis

Concerning the risk of QT prolongation induced by mirabegron, the expert advisors commented that deliberate actions are needed for possible fatal adverse events because mirabegron is a drug for QOL improvement, and thus it is insufficient to provide only cautions against the risk. In addition, there were the other opinions that it would be practically difficult in clinical practice to mandate periodic ECG examinations for all OAB patients treated with mirabegron, and also it may be difficult for urologists to determine whether or not ECG examination was necessary. In addition, the following findings were listed as the risks of QT/QTc prolongation and arrhythmogenesis: (a) the non-clinical data have shown that both unchanged mirabegron and its metabolites in plasma have hERG current inhibitory action, which is related to QT prolonged; (b) in the thorough QT/QTc study, 5.4% of the female subjects at the dose of 200 mg experienced

QTc prolonged with the change >30 ms, although none of the subjects experienced QTc >480 ms or the change in QTc >60 ms; (c) in the Japanese and foreign clinical studies, no adverse events related to TdP and QT prolonged were observed following administration of mirabegron, but patients on medication causing QT prolongation and patients with long QT syndrome were excluded; and (d) mirabegron has an agonistic effect not only on β_3 -adrenoceptors but also on β_1 - and β_2 -adrenoceptors. The effects on the latter receptors are weak but can increase the heart rate, and thus it cannot be ruled out that potential long QT syndrome may manifest. Hence, the risk-benefit balance over such risks was discussed taking into account that mirabegron is a drug for QOL improvement. As a result, the expert advisors commented that it should be advised that mirabegron be administered with extreme care in patients with predisposition to QT prolongation and patients on concomitant medication causing QT prolongation and that mirabegron be administered with care in patients with underlying cardiac diseases and patients with hypokalaemia. More specifically: (i) patients with long QT syndrome and patients on concomitant medication known to cause QT prolongation should undergo ECG examinations before the start of the treatment and then periodically during the treatment to check QT interval; (ii) mirabegron should be administered with care in patients with underlying cardiac diseases and patients with hypokalaemia; (iii) to inform the users that female patients have a higher risk of QT prolongation than male patients, data from the thorough QT/QTc study should be provided; and (iv) it is necessary to collect information about adverse events related to QT prolongation and TdP via the post-marketing surveillance. The expert advisors reached a consensus on the above opinions. Furthermore, PMDA has concluded that flecainide acetate and propafenone hydrochloride, which are antiarrhythmic drugs and substrates of CYP2D6, should be listed in “Contraindications for concomitant use” section, since mirabegron has a CYP2D6 inhibitory effect. For the above PMDA’s conclusion, the expert advisors commented that it is not necessary to dare to use such drugs concomitantly with caution from a viewpoint of the risk-benefit balance, other drugs are available according to the current guideline for antiarrhythmic pharmacotherapy, or therapeutic drugs other than mirabegron are also available if patients want to use continuously these antiarrhythmic agents. The conclusion of PMDA have been supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to include the following precautions in the package insert.

- The following statement should be included in the “Careful Administration” section: “(1) Patients with long QT syndrome including patients treated with antiarrhythmic drugs of Class IA (quinidine, procainamide, etc.) or Class III (amiodarone, sotalol, etc.) [see “Important Precautions” section].”
- The following statement should be included in the “Careful Administration” section: “(2) Patients susceptible to arrhythmia such as severe bradycardia or arrhythmia such as acute myocardial ischaemia (Ventricular tachycardia [including Torsades de pointes] and QT prolongation may occur.)”
- The following statement should be included in the “Careful Administration” section: “(3) Patients with hypokalaemia (Ventricular tachycardia [including Torsades de pointes] and QT prolongation may occur.)”
- The following statement should be included in the “Important Precautions” section: “(1) “QT prolongation associated with mirabegron may occur. For patients with cardiovascular diseases, caution should be exercised to the cardiovascular conditions by ECG examinations before starting the treatment with mirabegron.”
- The following statement should be included in the “Important Precautions” section: “(2) ECG examinations should be performed periodically for patients considered to be at a high risk of QT prolongation such as patients with a history of QT prolonged or arrhythmia and patients treated with drugs known to cause QT prolongation such as antiarrhythmic drugs of Class IA (quinidine, procainamide, etc.) or Class III (amiodarone, sotalol, etc.).”
- Specific information about the data from Study CL-037 and Study CL-077 for thorough

QT/QTc in terms of the risk of QT prolongation induced by mirabegron, including the finding that the risk of QT prolongation may differ between male and female subjects, should be provided in the “PHARMACOKINETICS” section.

The applicant responded that the above cautions will be included in the package insert, and PMDA accepted the applicant’s response.

b. Cardiovascular adverse events other than QT/QTc prolongation and arrhythmogenesis

In the Japanese clinical studies (Study CL-045, Study CL-048, Study CL-051), treatment experience with mirabegron in patients with organic cardiac diseases is limited. If mirabegron is approved, a possibility that the conditions are aggravated due to the increase of heart rate following administration of mirabegron to patients with underlying cardiac diseases such as angina pectoris and cardiac failure in clinical practice cannot be ruled out and mirabegron may be widely administered to elderly patients with concurrent diseases including cardiovascular ones continuously for an extended period. Based on the above findings, PMDA concluded that patients with serious cardiac diseases should be listed in the “CONTRADICTIONS” section, catecholamine preparations should be listed in the “Precautions for concomitant use” section, and more careful actions should be taken. PMDA’s conclusion has been supported by the expert advisors.

Based on the discussion at the Expert Discussion, PMDA instructed the applicant to include the following caution in the package insert and to list the catecholamine preparations in the “Precautions for concomitant use” section.

[CONTRADICTIONS (Mirabegron is contraindicated in the following patients.)]

- (2) Patients with serious cardiac diseases (Heart rate increased has been reported, and the symptoms may be aggravated.)

The applicant responded that the above caution will be included in the package insert and the catecholamine preparations will be listed in the “Precautions for concomitant use” section. PMDA accepted the applicant’s response.

(2).2) Use in patients with BPH

From the urodynamic data, PMDA considers that currently available information is insufficient to conclude that administration of mirabegron should be restricted on all of the patients with BOO secondary to BPH etc. However, in consideration that patients with BOO were listed in the exclusion criteria for the Japanese clinical studies in OAB patients and that treatment experience in these patients is limited, it is necessary to continue to pay attention to the safety information in these patients. The above conclusion of PMDA has been supported by the expert advisors.

Based on discussion at the Expert Discussion, PMDA asked the applicant to provide cautions to patients with concurrent BOO through the package insert. The applicant responded that the following statement will be included in the “Important Precautions” section: For patients with concurrent BOO (secondary to BPH etc.), treatment for the concurrent disease should be prioritized. PMDA accepted the applicant’s response.

The expert advisor commented that there are concerns about effects of concomitant use of mirabegron with 5 α -reductase inhibitors, which are used as therapeutic drugs for BPH in Japan, on reproductive organs, because the effects of mirabegron on reproductive organs have not been ruled out. In consideration that 5 α -reductase inhibitors and mirabegron may be concomitantly used in clinical practice, PMDA asked the applicant to consider providing a caution for concomitant use of these drugs.

The applicant responded as follows:

Since no study with concomitant use of mirabegron with 5 α -reductase inhibitors, which are therapeutic drugs for BPH, has been conducted, the safety, efficacy, and drug interaction following concomitant use of mirabegron with 5 α -reductase inhibitors remain unclear. However, since animal studies on mirabegron showed seminal vesicle and prostate atrophy, it cannot be ruled out that mirabegron may affect the reproductive organs. For 5 α -reductase inhibitors, not only their primary action but also the effects on reproductive organs (potentially suppressing the normal development of reproductive organs in male fetuses) and adverse drug reactions such as erectile dysfunction and breast disorder were observed. Thus, concomitant use of the two drugs may increase the effects on reproductive organ system. Therefore, the applicant will provide a caution in the “2. Important Precautions” section of “Precautions” in the package insert (draft), stating that “The safety and clinical effects of concomitant use of mirabegron with 5 α -reductase inhibitors have not been established at present. It is desirable to avoid concomitantly using mirabegron with 5 α -reductase inhibitors, which affect the production and metabolism of steroids.” In addition, similar cautions may be needed for concomitant use of mirabegron with drugs with 5 α -reductase inhibitory effect, not limited to the therapeutic drugs for BPH. Since 5 α -reductase inhibitors indicated for BPH and mirabegron may be concomitantly used in clinical practice, the applicant will identify the actual condition for concomitant use of mirabegron with 5 α -reductase inhibitors and collect the relevant safety information through the post-marketing surveillance.

PMDA accepted the applicant’s response.

(2).3) Effects on eyes

After the filing of the application in Japan, glaucoma occurred in a foreign long-term treatment study (Study CL-049). To evaluate effects of mirabegron on intraocular pressure, a clinical study is ongoing overseas in accordance with the direction of a foreign regulatory authority. However, at present, information about changes in the intraocular pressure after administration of mirabegron for an extended period is incomplete. Although the applicant determined that mirabegron dose not increase the intraocular pressure in humans, PMDA has concluded that the applicant’s claim is not appropriate. Concerning the PMDA’s conclusion, the following comments were raised from the expert advisors: (i) the relevant caution will be needed at least until the data from the currently ongoing additional clinical study in the US become available; (ii) before clinical development of mirabegron, which affects adrenoceptors, ophthalmological examinations should have been adequately implemented; and (iii) although non-clinical data showed distribution of mirabegron into eyes, data on the accumulation in eyes or the species difference are not available. On the other hand, the following comments were also presented: (i) it would be difficult to decide when to indicate ophthalmological examinations in clinical practice; and (ii) it may not be necessary to mandate the periodic ophthalmological examinations. Since patients with glaucoma undergo ophthalmological examinations periodically, it is considered possible to mandate the periodic ophthalmological examinations at least for such patients. In consideration of the above, the expert advisors reached a consensus that it is necessary to provide a caution that patients with glaucoma should undergo ophthalmological examinations periodically. Furthermore, the expert advisor has commented that there are plans to conduct post-marketing surveillance in approximately 10,000 patients, which may include patients with glaucoma to some extent, and thus it is necessary to continue to collect the relevant information available at the clinics where mirabegron is prescribed.

In consideration of the above discussion at the Expert Discussion, PMDA instructed the applicant to provide the following cautions in the package insert.

[PRECAUTIONS]

1. Careful Administration (Mirabegron should be administered with care in the following

patients.)

- (6) Patients with glaucoma (Intraocular pressure increased and/or aggravated symptoms may occur.)
- 2. Important Precautions
 - (5) When mirabegron is administered to patients with glaucoma, ophthalmological examinations should be performed periodically.

The applicant responded that the above cautions will be provided, and PMDA accepted the applicant's response.

(2).4) Incidence of tumorigenesis

Concerning tumorigenesis in patients treated with mirabegron, the expert advisors have supported the following PMDA's conclusion: although currently available data show no definite effects of mirabegron on incidence of malignant tumors, the risk of malignant tumors associated with the further long-term treatment remains unknown in consideration that the maximum duration of the treatment implemented so far is only 52 weeks; and therefore, it is necessary to continue to collect relevant information through research reports in Japan and overseas even after marketing. In addition, an expert advisor commented that the effect of mirabegron on tumor vessels should be investigated. In response to this opinion, PMDA asked the applicant to explain the effect of mirabegron on tumor vessels and to continuously collect relevant information through research reports in Japan and overseas even after marketing.

The applicant responded as follows:

The effect of mirabegron on tumor vessels has not been evaluated in non-clinical studies, and the literature search has not identified any report on effects of β_3 -adrenoceptor agonists on tumor vessels. It has been reported that catecholamines such as norepinephrine and epinephrine enhance growth of multiple types of malignant tumor by increasing biosynthesis of angiogenesis-inducing factors such as vascular permeability factor (VPF) and vascular endothelial growth factor (VEGF) through β_1 - and β_2 -adrenoceptors. The role of β_3 -adrenoceptors in this mechanism remains unknown. Concerning the risk of malignant tumors, the applicant plans to obtain the relevant observation data over a longer period than that of clinical data through post-marketing surveillance, the specified use-results survey on the long-term use, in which the observation period is set at up to 2 years. In addition, the relevant information will be continuously collected through research reports in Japan and overseas.

PMDA accepted the applicant's response.

(3) Risk of mirabegron based on non-clinical data

(3).1) Effects on reproductive organs

Effects of mirabegron on reproductive organs are critical as a risk of long-term treatment of a drug mainly intended to improve the quality of life (QOL). In association with this, PMDA has concluded that for clinical use of mirabegron, it is necessary to describe the above findings in non-clinical studies in the "Warnings" or "Important Precautions" section as well as to clearly state that the administration should be avoided in patients of reproductive age. Although the applicant claimed that the findings on reproductive organs were changes secondary to aggravated clinical conditions or decreased body weight, and thus had little toxicological significance, the applicant did not address the following questions: (i) why aggravated clinical conditions and decreased body weight occur?; (ii) on what basis, the applicant determined that the findings on reproductive organs were changes secondary to aggravated clinical conditions or decreased body weight; and (iii) if they were secondary changes, on what basis, the applicant determined that they had little toxicological significance. Based on the above, the following comments on the PMDA's conclusion were raised from the expert advisors: (i) mechanism of their development remaining unknown; (ii) although atrophy of reproductive organs suggested effects on synthesis and

metabolism of steroids, the applicant has not conducted the investigation to make clear such concerns, and thus it cannot be ruled out; (iii) if the possible effects on synthesis and metabolism of steroids are excluded, serious developmental toxicity may occur, which can indicate that the relevant risk is high for a drug which will be used for an extended period to improve QOL; and (iv) OAB patients are mostly middle aged or older, the caution that administration should be avoided for patients of reproductive age in clinical practice may be acceptable. The expert advisors reached a consensus that it is appropriate to avoid the administration to males and female patients of reproductive age, in consideration of the risk-benefit balance.

PMDA instructed the applicant to describe in the “Warnings” section the findings on reproductive organs in the non-clinical studies as well as that administration should be avoided for patients of reproductive age as follows:

[WARNING]

Administration of mirabegron should be avoided for patients of reproductive age wherever possible (in animals studies [rats], effects on reproductive organs such as decreased weights or atrophy of seminal vesicle, prostate, and uterus were observed, and at a high dose, extended diestrus and decreased implantation sites and live fetuses associated with decreased corpora lutea were observed).

The applicant responded that the above cautions will be provided, and PMDA accepted the applicant’s response.

(3.2) Effects on fetuses and offspring

In a non-clinical study of mirabegron, developmental delay, such as low fetal weight and delayed ossification, was observed and the findings cannot be overlooked. Taking into account that mirabegron is a drug for QOL improvement by suppressing OAB symptoms, PMDA has concluded that the risk in fetuses may largely outweigh the benefit for the mothers, and thus the use of mirabegron in pregnant women should be contraindicated. Then, for the PMDA’s conclusion, the following comments were raised from the expert advisors: (i) attention should be paid to that abnormal findings in rats and rabbits are related to the β -adrenoceptor agonistic effect, pharmacological action of mirabegron, and it is clear that mirabegron has teratogenicity in rabbits, thus, at present, an expert advisor supported the PMDA’s conclusion; and (ii) it is appropriate that PMDA has concluded that the use of mirabegron in pregnant woman be contraindicated, because the applicant’s claim that the fetotoxicity in rabbits was partially related to species differences in production amount of metabolite M5 remains a matter of speculation, and their claim that low fetal weight and delayed ossification were reversible is not appropriate due to lack of detailed investigation for the species difference.

Based on discussion at the Expert Discussion, PMDA instructed the applicant to contraindicate mirabegron for pregnant woman and to describe findings related to embryo-fetal development specifically.

The applicant responded that the following descriptions will be included in the package insert.

[CONTRAINDICATIONS (Mirabegron is contraindicated in the following patients.)]

- (3) Pregnant women and women who may possibly be pregnant (see “Use during Pregnancy, Delivery, or Lactation”)

[PRECAUTIONS]

6. Use during Pregnancy, Delivery, or Lactation
 - (1) Pregnant women

Mirabegron should not be used in pregnant woman or in women who may possibly be pregnant. (In animal studies [rats, rabbits], increased postimplantation embryonic loss, low body weight, increased bent scapula and wavy ribs, delayed ossification [decreased ossification of the sternbrae, metacarpal bone, phalanx media], aortic dilatation and increased cardiomegaly, and loss of accessory lung lobe were observed in fetuses.)

PMDA accepted the applicant's response.

(3).3) Excretion of mirabegron into milk

In a study where mirabegron was administered to pregnant rats, low 4-day survival rate of offspring and reduced body weight gain were observed, and in the other non-clinical study in rats, mirabegron-derived radioactivity was distributed into milk at the radioactivity level more than that in dam plasma. It cannot be ruled out that toxicological findings in rat offspring may be related to mirabegron-derived substances distributed into milk. In consideration of the above, PMDA has concluded that it is appropriate to consider the other therapeutic options for lactating women. The expert advisors supported the PMDA's conclusion and raised the comment that the risk is high for a drug which will be used for an extended period to improve QOL, and thus the drug should be contraindicated for not only pregnant women but also lactating women. The expert advisors finally reached a consensus that mirabegron should be contraindicated for lactating women.

Based on discussion at the Expert Discussion, PMDA instructed the applicant to list lactating women in the "Contraindications" section in the package insert and to describe risks potentially occurring as a consequence of lactating specifically. The applicant replied that the following description will be provided.

[CONTRAINDICATIONS (Mirabegron is contraindicated in the following patients.)]

- (4) Lactating women (Animal studies [rats] have shown that mirabegron is excreted in breast milk. Following administration of mirabegron to lactating dams, low survival rate and reduced body weight gain were observed (see the "Use during Pregnancy, Delivery, or Lactation" section))

[PRECAUTIONS]

6. Use during Pregnancy, Delivery, or Lactation

(2) Lactating women:

Mirabegron should not be used in lactating women (Animal studies [rats] have shown that mirabegron is excreted in breast milk. Following administration of mirabegron to lactating dams, low survival rate and reduced body weight gain were observed.)

PMDA accepted the applicant's response.

(4) Clinical positioning

PMDA has concluded that mirabegron could be a therapeutic option for OAB, but mirabegron is not a drug positioned as the first-choice medication for OAB with precedence over anticholinergics. Concerning the PMDA's conclusion, the expert advisors raised the following comments: (i) mirabegron may not be positioned as a first-line medication for OAB immediately; (ii) the current first-line medication is anticholinergics, and in clinical practice, mirabegron may be considered only for patients who have not responded to initial anticholinergics or who have safety issues with initial anticholinergics; (iii) and at present, mirabegron should be positioned as the second-line medication from a safety point of view. The expert advisors finally reached a consensus on the following conclusion: Although mirabegron does not have to be used as the second-line medication, limiting to patients who have not sufficiently responded to

anticholinergics, since mirabegron is a drug with a new mechanism of action and may have various potential risks, careful administration is required depending on conditions of the patient.

(5) Indications

PMDA has concluded that the proposed indications of mirabegron, “Urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder” are appropriate for indications. PMDA’s conclusion was supported by the expert advisors.

(6) Dosage and administration

(6.1) Dosage and administration

PMDA has concluded that it is appropriate to set the dosage and administration as “The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal.” PMDA’s conclusion was supported by the expert advisors.

(6.2) Use in patients with renal impairment or hepatic impairment

Based on the data from the pharmacokinetic study in patients with renal impairment (Study CL-038) and pharmacokinetic study in patients with hepatic impairment (Study CL-039), PMDA has concluded that it is appropriate to reduce the starting dose to an half (25 mg) of the regular dose (50 mg) for patients with moderate hepatic impairment and patients with severe renal impairment, but not to assume the dose increase for those patients, and to provide a caution in the “Careful Administration” section. PMDA’s conclusion was supported by the expert advisors. In addition, PMDA’s conclusion that information about those patients should be collected appropriately after the market launch and actions should be taken where necessary.

Based on discussion at the Expert Discussion, PMDA instructed the applicant to include appropriate descriptions in the “Precautions for Dosage and Administration” section for patients with renal or hepatic impairment. The applicant responded that the following description will be provided.

[DOSAGE AND ADMINISTRATION]

Precautions for Dosage and Administration

- (1) For patients with moderate hepatic impairment (Child-Pugh score, 7-9), administration of mirabegron should be initiated at the dose of 25 mg once daily. (In patients with hepatic impairment, the blood concentration may be increased. [see “Careful Administration” and “Pharmacokinetics”])
- (2) For patients with severe renal impairment (eGFR, 15-29 mL/min/1.73 m²), administration of mirabegron should be initiated at the dose of 25 mg once daily. (In patients with renal impairment, the blood concentration may be increased [see “Careful Administration” and “Pharmacokinetics”].)

PMDA accepted the applicant’s response.

(6.3) Concomitant use with anticholinergics

Even though the applicant could have assumed even at the development stage that mirabegron may be used concomitantly with anticholinergics, which are existing therapeutic drugs for OAB and have a different mechanism of action, in patients who did not sufficiently responded to mirabegron or anticholinergics, the applicant did not investigate the efficacy and safety of mirabegron used concomitantly with anticholinergics at the development stage, and thus, it is not desirable to use mirabegron concomitantly with anticholinergics in clinical practice without caution. Therefore, PMDA has concluded that it is appropriate to provide an explicit caution that concomitant use of mirabegron with anticholinergics should be avoided. Concerning the PMDA’s conclusion, the following comments were raised from the expert advisors: (i) the applicant should be requested to collect data on concomitant use of mirabegron with anticholinergics; (ii) in the

first place, the applicant should have investigated the efficacy and safety of the concomitant use before the filing of the application; and (iii) the applicant should be responsible for the caution against the concomitant use at present, but in the future, the concomitant use of mirabegron with anticholinergics should be investigated for refractory patients. The expert advisors reached a consensus that the applicant should be requested to conduct post-marketing clinical studies for evaluating the efficacy and safety of mirabegron used concomitantly with anticholinergics and then provide relevant information immediately in clinical practice.

Based on the discussion at the Expert Discussion, PMDA considers that the applicant should conduct post-marketing clinical studies to evaluate the efficacy and safety of mirabegron used concomitantly with anticholinergics in Japanese OAB patients. The applicant should design the post-marketing clinical studies paying attention to that anticholinergics used as a comparator include CYP2D6 substrates potentially involved in drug-drug interactions of mirabegron and those with the risk of QT prolongation.

PMDA asked the applicant to conduct post-marketing clinical studies in an appropriate design to evaluate the efficacy and safety of mirabegron used concomitantly with anticholinergics in Japanese OAB patients.

The applicant responded as follows:

Mirabegron may be used concomitantly with anticholinergics with a different mechanism of action in patients who have not sufficiently responded to mirabegron or anticholinergics. Therefore, post-marketing clinical studies will be performed to evaluate the efficacy and safety of mirabegron used concomitantly with anticholinergics in Japanese OAB patients immediately after the approval. The applicant will thoroughly deliberate what design can be eligible to evaluate the efficacy and safety appropriately and then also seek advice of PMDA on that. In addition, since anticholinergics include CYP2D6 substrates potentially involved in drug interactions of mirabegron and drugs with the risk of QT prolongation, the applicant will, before designing the post-marketing clinical studies, investigate the drug interactions between mirabegron and a concomitant anticholinergic as well as the risk of QT prolongation induced by such concomitant use. Then, the applicant will conduct the studies to evaluate the efficacy and safety of concomitant use of mirabegron with anticholinergics potentially acceptable for the concomitant use.

At present, PMDA has accepted the applicant's response that post-marketing clinical studies will be conducted, but will discuss the details of the studies in the future.

(6.4) Concomitant use with α_1 receptor antagonists in patients with BPH

Concerning concomitant use of mirabegron with α_1 receptor antagonists, PMDA has concluded that it may not be necessary to restrict use of mirabegron in all of the patients with BPH, but treatment experience with such concomitant use is limited. Therefore, it is necessary to continue to pay attention to the safety of such concomitant use. PMDA's conclusion was supported by the expert advisors.

PMDA asked the applicant to identify the actual conditions for concomitant use and to collect the relevant safety information through the post-marketing surveillance, and thus to take actions such as provision of cautions if found necessary based on the obtained information.

The applicant responded as follows:

As the primary surveillance items of the use-results survey in the post-marketing surveillance plan (outline), the applicant will identify information about the actual conditions for concomitant use of mirabegron with α_1 receptor antagonists, and evaluate the safety and efficacy of such concomitant use, and then take measures such as revision of Precautions section where necessary.

PMDA accepted the applicant's response.

(7) Drug interaction (interactions mediated by CYP2D6 inhibitory action of mirabegron)

Concerning cautions for concomitant use of mirabegron with CYP2D6 substrates, PMDA has concluded that flecainide acetate and propafenone hydrochloride should be contraindicated. PMDA's conclusion was supported by the expert advisors [see "(2) Safety, 1) Cardiovascular risk"]. The following comments were raised from the expert advisors: (i) drugs of which blood concentration was actually found to be increased should be made clear; and (ii) it would be necessary to provide information about what drugs act as CYP2D6 substrate.

PMDA instructed the applicant to list antiarrhythmic drugs acting as CYP2D6 substrates (flecainide acetate, propafenone hydrochloride) in the "Contraindications for concomitant use" section and provide appropriate descriptions in the Interactions section. The applicant responded that they will take relevant actions in the package insert (draft) to contraindicate mirabegron for patients treated with flecainide acetate or propafenone hydrochloride, and will list both drugs in the "Contraindications for concomitant use" section. PMDA accepted the applicant's response.

(8) Post-marketing actions

PMDA considers as follows:

In consideration that mirabegron is a drug with a new mechanism of action and the use experience in Japan and overseas is limited, collection of the safety information from clinical settings is important, and it is appropriate to conduct not only the use-results survey but also specified use-results survey for the long-term safety. It is also necessary to investigate the clinical course in patients with hypertension and elderly patients and effects of concomitant drugs, and thus details of such investigations need to be examined. Concerning QT prolongation and glaucoma, the applicant explained that information will be obtained from the foreign clinical studies conducted based on the discussion with the FDA. However, their risks have not been ruled out so far, it is a problem not to include these matters in the survey plan in Japanese patients. Therefore, PMDA has concluded that the applicant should include the surveillance items related to QT prolongation and glaucoma in the concerned post-marketing surveillance and continue to collect the relevant information even after marketing.

The above conclusion of PMDA was supported by the expert advisors.

Based on the discussion at the Expert Discussion, PMDA instructed the applicant to examine the post-marketing surveillance protocol including the following points.

- Collect information about adverse events related to QT prolongation and TdP as well as collect data of ECG performed on patients with QT prolongation potential
- Collect information about incidence of glaucoma and ophthalmological examination results obtained from glaucoma patients treated with mirabegron. Design the survey to enrol those patients to a certain number, and then take measures to ensure smooth information collection by preparing a patient diary, etc.
- Since experience of concomitant use of mirabegron with α_1 receptor antagonists is limited, identify the actual conditions for concomitant use of these drugs and collect the relevant safety information through the post-marketing surveillance. Take actions such as provision of cautions if found necessary based on the obtained information.
- In consideration that currently available data show no definite effects of mirabegron on incidence of malignant tumors, and that the maximum duration of the treatment implemented so far is only 52 weeks, the risk of malignant tumor associated with the further long-term treatment remains unknown. Therefore, continue to collect relevant information through research reports etc. in Japan and overseas even after marketing.

The applicant responded as follows:

The applicant will take actions on the above points appropriately. In addition, use-results survey will be conducted to identify the actual conditions for concomitant use of mirabegron with 5 α -reductase inhibitors, which may occur in patients with BPH, and to evaluate the relevant safety. Since the possibility that β_3 agonistic effect affects glucose metabolism cannot be ruled out, the applicant will extract patients with concurrent diabetes mellitus from the survey population according to the concurrent diseases and concomitant medications and then evaluate the safety and efficacy by patient demographics. Furthermore, as use-results survey to identify information about the incidence of adverse drug reactions in actual conditions of clinical practice as well as factors potentially affecting the safety and efficacy, the applicant submitted the draft outline of the post-marketing surveillance plan with target sample size of 10,000 patients, 12-week observation period, and 3-years surveillance period, including the specified use-results survey with the following primary surveillance items and the long-term treatment.


Primary surveillance items

- Safety and efficacy in the patients with hepatic impairment and the patients with renal impairment
- Safety and efficacy of mirabegron used concomitantly with other drugs (α_1 receptor antagonists, anticholinergics, 5 α -reductase inhibitors, potent CYP3A4 inhibitors, CYP3A4 inducers, drugs mainly metabolized by CYP2D6, commonly used drugs)
- Incidence of cardiovascular adverse events

Since mirabegron may be used concomitantly with anticholinergics with a different mechanism of action in patients who have not sufficiently responded to mirabegron or anticholinergics, the post-marketing clinical studies in Japanese OAB patients will be conducted to evaluate the efficacy and safety of concomitant use of mirabegron with anticholinergics. In addition, concerning anticholinergics used concomitantly in the post-marketing clinical studies, the applicant will investigate the drug interactions between mirabegron and a concomitant anticholinergic as well as the risk of QT prolongation induced by such concomitant use in advance to select anticholinergics potentially acceptable for the concomitant use [see “(6) Dosage and administration, 3) Concomitant use of anticholinergics”].

Considering that the post-marketing surveillance plan submitted as a response by the applicant is almost appropriate, PMDA has accepted the applicant’s response. In addition, since it is important to communicate information about the safety and proper use of mirabegron, PMDA will examine the details of the post-marketing surveillance plan and post-marketing clinical study protocol as well as the details of post-marketing risk management in the future.

(9) Reworking in Step 3 of the manufacturing process of the drug substance

 PMDA thus asked the applicant to remove the concerned reworking from the manufacturing process. The applicant responded that the reworking process will be removed, accordingly, PMDA accepted the applicant’s response.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA’s conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory

review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.2-1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of its review, PMDA concludes that the product may be approved for the indication and the dosage and administration as shown below. The re-examination period is 8 years, the drug substance is classified as a poisonous drug and the drug product is classified as a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]	Urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder
[Dosage and administration]	The usual adult dosage is 50 mg of mirabegron administered orally once daily after a meal.