Report on the Deliberation Results

February 5, 2010

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

[Brand name]	Rozerem Tablets 8 mg
[Non-proprietary name]	Ramelteon (JAN*)
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	February 29, 2008

[Results of deliberation]
In the meeting held on January 29, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

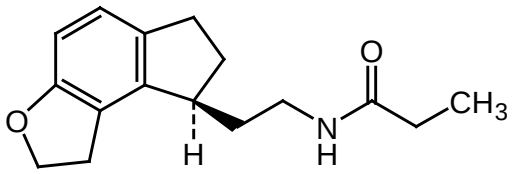
**Japanese Accepted Name (modified INN)*

Review Report

January 15, 2010
Pharmaceuticals 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] Rozerem Tablets 8 mg
[Non-proprietary name] Ramelteon
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] February 29, 2008
[Dosage form/Strength] Tablets: each tablet contains 8 mg of Ramelteon
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Empirical formula: $C_{16}H_{21}NO_2$
Molecular weight: 259.34
Chemical name: *N*-{2-[(8*S*)-1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl]ethyl}propanamide

[Items warranting special mention] None
[Reviewing office] Office of New Drug III

Review Results

January 15, 2010

[Brand name] Rozerem Tablets 8 mg
[Non-proprietary name] Ramelteon
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] February 29, 2008
[Results of review]

Based on the submitted data, the efficacy of the product in improving sleep-onset insomnia has been demonstrated and its safety is considered acceptable in view of its observed benefits. The relationship of the presence or absence of prior therapy with other hypnotics or the duration of disease with the efficacy and safety of the product, the occurrence of impaired consciousness (memory impairment during interim periods of wakefulness, etc.), the occurrence of withdrawal symptoms, rebound insomnia, abuse and dependence, and muscle relaxation such as staggering, which are problematic events associated with currently marketed hypnotics, and the impact of the product on next-day functioning etc. need to be further investigated via post-marketing surveillance.

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 and dosage and administration.

[Indication]
Improvement of sleep-onset insomnia

[Dosage and administration]
The usual adult dose is 8 mg as Ramelteon taken orally at bedtime.

Review Report (1)

November 27, 2009

I. Product Submitted for Registration

[Proposed brand name] Rozerem Tablets 8
[Non-proprietary name] Ramelteon
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] February 29, 2008
[Dosage form/Strength] Tablets: each tablet contains 8 mg of Ramelteon
[Proposed indication] Insomnia
[Proposed dosage and administration]
The usual adult dose is 8 mg as Ramelteon taken orally at bedtime.

II. Summary of the Submitted Data and Outline of Review by 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.

Currently, for the treatment of insomnia, benzodiazepine (BZD) and nonbenzodiazepine (non-BZD) hypnotics have been used, and these agents work by binding to the $GABA_A$ receptor in the central nervous system and by promoting central nervous system depression (Miura S, Consulting ed. *An outline of antipsychotic agents*, Rev ed. 2001, Vol 2. Seiwa Shoten Co., Ltd., Tokyo, Japan; 2001), but reducing their adverse reactions, e.g. dependence, amnesia, residual effects, muscle relaxation, rebound insomnia, and withdrawal syndrome, is considered a future challenge (Uchimura M, Chief Researcher, MHLW-sponsored research project on psychiatric/neurological disorders, *Research Project Report for FY 1999-2001: Development of guidelines for the diagnosis and treatment of sleep disorders and its empirical research*, 2002; 61-66).

The active ingredient of the product, Ramelteon, is a selective melatonin MT_1 and MT_2 receptor agonist discovered by Takeda Pharmaceutical Company Limited in 1996. Clinical trials were initiated in [redacted] 19[redacted] in Japan and in [redacted] 19[redacted] overseas. Since its U.S. approval in July 2005, the product has been approved in 4 countries as of October 2009.

As the efficacy and safety of the product in patients with insomnia have been confirmed, the applicant has filed a marketing application.

Although the proposed brand name was “Rozerem Tablets 8,” it was requested that the brand name should clearly indicate the strength of the active ingredient, and then the applicant explained that the proposed brand name would be changed to “Rozerem Tablets 8 mg” and PMDA accepted it.

In the EU, a marketing authorization application for Ramelteon was submitted in March 2007. However, the European Medicines Agency (EMA) issued a negative opinion for granting a marketing authorization to Ramelteon in June 2008, and the application was withdrawn in September 2008 [for the situation in the EU, see “4.(iii).B.(4) Reasons and other factors for refusal of authorization in the EU”].

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The Ramelteon drug substance is a white crystalline powder. Its general properties including description, solubility, hygroscopicity, melting point and [redacted], specific rotation, partition coefficient, and crystalline polymorphism have been determined. Ramelteon is not hygroscopic and has no polymorphs.

The manufacturing process for the drug substance uses [redacted] as starting materials and consists of Step 1 [redacted] synthesis), Step 2 ([redacted] synthesis), Step 3 [redacted]), Step 4 ([redacted] synthesis), Step 5 ([redacted]), and Step 6 [redacted]) and reprocessing procedures have been established for Step [redacted], Step [redacted], and Step [redacted]. Step [redacted], Step [redacted], and Step [redacted] have been defined as critical steps and [redacted] and [redacted] have been defined as critical intermediates and their control parameters and action limits have been established.

The chemical structure of the drug substance has been elucidated by elementary analysis, mass spectrometry, ultraviolet-visible (UV) spectroscopy, infrared (IR) spectrophotometry, nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), optical rotation, isomerism, crystalline polymorphism, and [redacted]. Ramelteon has one chiral center and is produced as the (*S*) form. Although the (*R*)-enantiomer exists, [redacted] in the drug substance and drug product and [redacted] has not been detected also in stability studies of the drug substance or drug product and [redacted]. Impurities including related substances, residual solvents, and [redacted] have been analyzed.

The proposed specifications for the drug substance include description, identification (UV spectrum, IR spectrum), purity [redacted], [redacted] [redacted], related substances [HPLC], residual solvents [redacted], [redacted], [redacted], and assay (HPLC). [redacted], [redacted], [redacted], [redacted], and [redacted] have also been determined, but are not included in the drug substance specification. The specification limits for related substances have been established for Related Substance 1, Related Substance 2, Related Substance 3, others (individual), and total related substances and the

specification limits for residual solvents have been established for Residual Solvent 1 and Residual Solvent 2.

In order to assess the stability of the drug substance, long-term testing (25°C/60% RH/dark place, 36 months) and accelerated testing (40°C/75% RH/dark place, 6 months) were performed on 3 pilot-scale drug substance batches primary packaged in low-density polyethylene bags. Using 1 pilot-scale drug substance batch, stress testing (temperature [°C/ , , months], temperature [°C/ , , months], humidity [°C/ % RH/ , , months], light [an overall illumination of not less than 1.2 million lx·h + an integrated near ultraviolet energy of not less than 200 W·h/m^2, petri dish (exposed or protected)]) was performed. The attributes to be tested in these studies include description, , identification (UV spectrum, IR spectrum), , , related substances (HPLC), , and assay (HPLC) and was also to be tested in long-term and accelerated testings. At the long-term, accelerated, and stress (humidity) storage conditions, there was no change over time for all attributes tested and the drug substance was stable. At the stress storage conditions (temperature), total related substances were increased and the major degradation product was Related Substance 4, which were within the specification ranges. At the stress storage conditions (light), related substances ([Related Substance 4, etc.],) were increased beyond the specification limits and the assay value was slightly decreased. Based on the above study results, a storage condition of “store at room temperature in well-closed containers” and a retest period of 3 years have been proposed for the drug substance.

2.A.(2) Drug product

The drug product is available as pale orange-yellow, film-coated tablets containing the drug substance, diluents, a disintegrant, binders, a lubricant, a coating agent, and colorants. The proposed commercial formulation contains 8 mg of the drug substance. The excipients are and no novel excipient is used. The tablets are supplied in PTP sheets (and aluminum foils) or bottles (glass bottles with metal caps).

The drug product has been designed as a film-coated tablet, since the drug substance is unstable to light. In clinical studies, besides the proposed commercial formulation, the 0.1, 1, 4, 8, and 10 mg tablet formulations containing different excipients from the proposed commercial formulation and the 4, 16, and 32 mg tablet formulations containing the same excipients as the proposed commercial formulation were used. The 4 mg tablet formulation used in a phase II/III study (5.3.5.1-2, CCT002) and the proposed commercial formulation showed comparable dissolution profiles, and other formulations were compared with the proposed commercial formulation based on the dissolution profiles or human pharmacokinetic data etc. [see “4.(i) Summary of biopharmaceutic studies and associated analytical methods”]

The manufacturing process for the drug product consists of Step 1 ( ), Step 2 ( ), Step 3 ( ), Step 4 ( ), Step 5 ( ), and Step 6 ( ) and Step , Step , and Step have been defined as critical steps and their control parameters and actionlimits have been established.

The proposed specifications for the drug product are description, identification (UV spectrum), purity (related substances [HPLC]), uniformity of dosage units (content uniformity), dissolution, and assay (HPLC). [redacted], [redacted], [redacted], and [redacted] have been determined, but are not included in the drug product specification. The specification limits for related substances have been established for [redacted] and total related substances.

In order to assess the stability of the drug product, long-term testing (25°C/60% RH/dark place, 36 months) and accelerated testing (40°C/75% RH/dark place, 6 months) were performed on the tablets produced at a pilot scale packaged in PTP sheets/cartons or glass bottles. Stress testing (temperature [[redacted]°C/[redacted], [redacted], [redacted] months], temperature [[redacted]°C/[redacted], [redacted], [redacted] months], humidity [[redacted]°C[redacted]% RH/[redacted], [redacted], [redacted] months], humidity [[redacted]°C[redacted]% RH/[redacted], [redacted], [redacted] months], light [an overall illumination of not less than 1.2 million lx·h + an integrated near ultraviolet energy of not less than 200 W·h/m^2, petri dish (exposed or protected)]) was also performed. The attributes to be tested in these studies include description, identification, [redacted], related substances, dissolution, assay, [redacted], and [redacted] and [redacted] was also to be tested in long-term and accelerated testings. At the long-term, accelerated, and stress storage conditions (temperature, [redacted]°C or [redacted]°C[redacted]), related substances were increased, which were within the specification ranges. For the tablets packaged in PTP sheets, [redacted] was increased and [redacted] was decreased, but there was no change over time for other attributes tested. The stress data (humidity [[redacted]°C/[redacted]%RH[redacted]]) showed increases in related substances, increased [redacted], and decreased [redacted]. At the stress storage conditions (humidity [[redacted]°C[redacted]% RH[redacted]], light), no significant change occurred for all attributes tested. Based on the above, a shelf-life of 3 years has been proposed for the drug product stored in PTP sheets or glass bottles at room temperature.

2.B. Outline of the review by PMDA

2.B.(1) Drug substance

In the stress testing (light) of the drug substance, related substances were increased beyond the specification limits. Thus, PMDA requested that the drug substance should be stored protected from light and the applicant explained that the new drug application will specify that the drug substance is stored protected from light.

2.B.(2) Drug product

In the stress testing of the drug product, [redacted] was increased and [redacted] was decreased at the high-humidity conditions. PMDA asked the applicant to explain the influence of humidity on the quality of the product and whether [redacted] and [redacted] should be included in the drug product specification.

The applicant explained as follows:

At the high-humidity stress conditions ([redacted]°C/[redacted]%RH/[redacted], [redacted], [redacted] months), although [redacted] was increased and [redacted] was decreased, there were no effects on dissolution and assay. Also, related substances were slightly increased, but they were within the specification ranges. Thus, in light of these factors, it is unlikely that the quality of the product is influenced by humidity. Therefore,

there is no need to include [redacted] and [redacted] in the drug product specification. Although it is anticipated that a decrease in [redacted] can lead to broken tablets during handling, when [redacted] as specified in General Information of the Japanese Pharmacopoeia was performed using the drug products with decreased [redacted] after being subjected to this stress testing, [redacted] was [redacted]%, which was at an acceptable level of not more than [redacted]%. Therefore, this will not become a major problem, and there is also no need to include a caution statement in the package insert.

PMDA accepted the above response and concluded that the proposed specification, storage conditions, and re-test period for the drug substance and the proposed specification, storage conditions, and shelf-life for the drug product are acceptable.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

Unless otherwise specified, the data are expressed as the mean ± standard error (SE).

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

3.(i).A.(1).1) *In vitro* studies

(a) Melatonin receptor binding affinity and inhibition of forskolin-induced cAMP production

In vitro receptor binding studies showed that the Ki values (pM for Mel_{1a}/Mel_{1c}, MT_1, and MT_2 receptors, nM for MT_3 binding site) at melatonin receptors (chick Mel_{1a}/Mel_{1c} receptor, human MT_1 and MT_2 receptors, hamster MT_3 binding site) were 23.1 ± 0.4, 14.0 ± 0.5, 112 ± 5.4, and 2650 ± 183, respectively, for Ramelteon, 368 ± 8.8, 80.7 ± 2.1, 383 ± 5.0, and 24.1 ± 0.5, respectively, for melatonin, and 24.8 ± 1.7, 13.1 ± 0.3, 188 ± 3.9, and 0.96 ± 0.02, respectively, for 2-iodomelatonin (Reference data 4.2.1.1-1, 4.2.1.1-2).

In Chinese hamster ovary cells (CHO cells) expressing the MT_1 or MT_2 receptor, Ramelteon, melatonin, and 2-iodomelatonin inhibited forskolin (1 μM)-stimulated cAMP production in a concentration-dependent manner and their IC_{50} values (pM) at the MT_1 receptor were 21.2 ± 5.4, 77.8 ± 14.6, and 26.8 ± 7.5, respectively and their IC_{50} values at the MT_2 receptor (mean with its 95% confidence interval [CI]) were 53.4 [40.7, 70.3], 904 [714, 1150], and 60.7 [44.0, 83.9], respectively (Reference data 4.2.1.1-1, 4.2.1.1-2).

At 0.03 to 0.3 nM, Ramelteon (0.001-0.3 nM) and melatonin (0.01-1 nM) concentration-dependently inhibited forskolin (1 μM)-stimulated cAMP production in the rat pituitary (Reference data 4.2.1.1-4).

(b) Affinities for other neurotransmitter receptors and effects on various enzyme activities (4.2.1.1-5)

The binding affinities of Ramelteon for neurotransmitter receptors[1)] were determined using *in vitro* receptor binding assays. As a result, Ramelteon (10 μM) demonstrated no affinity for any of the receptors tested while melatonin (10 μM) exhibited affinity for the 5-HT_{1A} receptor with a Ki value of 5.6 μM. Ramelteon or melatonin (both 10-1000 μM) did not show ≥50% inhibition of the activity of any of ≥50 different enzymes[2)] tested.

3.(i).A.(1).2) *In vivo* studies

(a) Effects on physiological nocturnal sleep in monkeys (4.2.1.1-6)

A single oral dose (p.o.) of Ramelteon, melatonin, or zolpidem was administered to monkeys within 10 minutes prior to the start of the dark period to characterize their effects on sleep and wakefulness (light NREM [Non-rapid eye movement] sleep [Stage 1 and Stage 2, Light Sleep: LS], slow wave sleep [Stage 3 and Stage 4, Slow Wave Sleep: SWS], REM [Rapid eye movement] sleep). Ramelteon (0.3 mg/kg) produced a decreased latency to SWS, but no significant reduction in latency to LS, and melatonin (1 mg/kg) or zolpidem (10 and 30 mg/kg) had no effect on latency to LS or SWS. While Ramelteon tended to increase total sleep time and SWS duration, melatonin had no effect on either total sleep time or SWS duration and zolpidem had no effect on total sleep time, but exhibited a trend towards increasing SWS duration at the high dose (30 mg/kg). The electroencephalograms (EEGs) during NREM sleep in the Ramelteon and melatonin groups were similar to those in the vehicle control group while fast waves were also present on the sleep EEGs of the zolpidem group. When a dose response of Ramelteon (0.003-0.3 mg/kg) or melatonin (0.3-3 mg/kg) was assessed, Ramelteon at 0.003 mg/kg exhibited a trend towards increased total sleep time, 0.03 mg/kg of Ramelteon produced a decreased latency to LS and SWS and an increased total sleep time, and 0.3 mg/kg of Ramelteon produced a decreased latency to SWS and exhibited a trend towards increased total sleep time.Melatonin at 0.3 mg/kg produced a decreased latency to LS and exhibited a trend towards increased total sleep time, and 3 mg/kg of melatonin exhibited a trend towards increased total sleep time. These results indicated no dose response of Ramelteon (≥0.03 mg/kg) or melatonin (≥0.3 mg/kg).

(b) Effects on sleep in cats (4.2.1.1-7)

Ramelteon (0.0001-0.1 mg/kg, p.o.) or melatonin (0.001-1 mg/kg, p.o.) was administered to cats in the morning to characterize their effects on sleep and wakefulness (wakefulness, SWS, REM sleep). Ramelteon at ≥0.001 mg/kg produced decreased wakefulness and increased SWS and Ramelteon at 0.1 mg/kg increased REM sleep. While 0.001 mg/kg of Ramelteon exerted an effect on wakefulness only at 6 hours after administration, at ≥0.01 mg/kg, effects on wakefulness were observed at 2, 4, and 6 hours after administration. Melatonin at ≥0.01 mg/kg produced increased SWS and 1 mg/kg of melatonin produced decreased wakefulness at 2 hours after administration.

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1) adrenergic α and β receptors, dopamine receptors, GABA receptors, glutamate receptors, histamine receptors, muscarinic receptors, opioid receptors, potassium channels, calcium channels, and serotonin receptors, etc.

2) acetyl CoA synthetase, acetylcholinesterase, cyclooxygenases, HMG-CoA reductase, NO synthase, phosphodiesterases, monoamine oxidases (MAO), and protein kinases, etc.

(c) Effects on circadian rhythm reentrainment after a phase shift (Reference data 4.2.1.1-8)

After rats were maintained on a 12-hour lights-on/lights-off cycle (light period from 7:00 to 19:00) for 21 days, followed by an 8-hour phase advance of light-dark cycle (light period from 23:00 to 11:00), Ramelteon (0.1or 1 mg/kg, p.o.) or melatonin (1 or 10 mg/kg, p.o.) was given immediately prior to the dark period to study their effects on circadian rhythm reentrainment. Compared to vehicle-treated rats, Ramelteon-treated rats and melatonin-treated rats exhibited a trend towards fewer days until the percentage of activity occurring in the dark period reached 90% after a phase advance of the light-dark cycle.

3.(i).A.(1).3) Pharmacologic actions of metabolites

(a) Melatonin receptor binding affinity and inhibition of forskolin-induced cAMP production

In vitro receptor binding studies showed that the Ki values (nM) for chick Mel_{1a}/Mel_{1c} receptor and hamster MT_3 binding site were >236 and >9000, respectively, for both M-I and M-IV (2*S*, 8*R*), 0.654 ± 0.0743 and >9000, respectively, for M-II (2*S*, 8*S*), 36.0 ± 1.23 and 6370 ± 263, respectively, for M-III, and 4.04 ± 0.0975 and 4570 ± 321, respectively, for M-V (4.2.1.1-3).

In CHO cells expressing the human MT_1 or MT_2 receptor, the Ki values of M-II (2*S*, 8*S*) (pM) were 114 ± 12.5 and 566 ± 13.1, respectively, and its IC_{50} values for the inhibition of forskolin (1 μM)-stimulated cAMP production (pM, mean with its 95% CI) were 208 [60.4, 850] and 1470 [930, 2380], respectively (4.2.1.1-2, 4.2.1.1-3).

(b) Affinities for other neurotransmitter receptors and effects on various enzyme activities (4.2.1.1-9)

The binding affinities of M-II (2*S*, 8*S*) (10 μM) for neurotransmitter receptors[1)] were determined using *in vitro* receptor binding assays. M-II (2*S*, 8*S*) exhibited affinity for the $5\text{-}HT_{2B}$ receptor with a Ki value of 1.75 μM but no affinity for other neurotransmitter receptors. M-II (2*S*, 8*S*) (10-1000 μM) did not show ≥50% inhibition of the activity of any of ≥50 different enzymes[2)] tested.

(c) Sleep-promoting action of metabolite M-II (2*S*, 8*S*) in cats (4.2.1.1-10)

M-II (2*S*, 8*S*) (0.001-1 mg/kg, p.o.) was administered to cats in the morning to characterize its effects on sleep and wakefulness (wakefulness, SWS, REM sleep). M-II (2*S*, 8*S*) at ≥0.01 mg/kg increased SWS and ≥0.1 mg/kg of M-II (2*S*, 8*S*) produced decreased wakefulness and effects on wakefulness were observed at 2, 4, and 6 hours after administration.

(d) Sleep-promoting action of metabolite M-II (2*S*, 8*S*) in monkeys (Reference data 4.2.1.1-11)

M-II (2*S*, 8*S*) (1-10 mg/kg, p.o.) was administered to monkeys within 10 minutes prior to the start of the dark period to characterize its effects on sleep and wakefulness (light NREM [Stage 1 and 2, LS], slow wave sleep [Stage 3 and 4, SWS], REM sleep). M-II (2*S*, 8*S*) at 3 mg/kg produced a decreased latency to LS and SWS and ≥3 mg/kg of M-II (2*S*, 8*S*) exhibited a trend towards increased total sleep time. In the EEG, no abnormal waveforms were detected at any of the doses and the EEG waveforms were similar to those obtained from unchanged Ramelteon-treated monkeys.

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

3.(i).A.(2).1) Effects on learning and memory (Reference data 4.2.1.2-1)

(a) Effects on water maze learning in rats

In a water maze learning experiment in rats, the impairment of learning and memory induced by Ramelteon (3-30 mg/kg, p.o.), melatonin (10-100 mg/kg, p.o.), diazepam (3-30 mg/kg, p.o.), or triazolam (0.1-1 mg/kg, p.o.) was assessed. Ramelteon or melatonin had no effect at any dose while diazepam at ≥10 mg/kg and triazolam at all doses reduced the number of crossings over the platform location in a probe test[3)] and diazepam at 30 mg/kg and triazolam at 1 mg/kg increased the escape latency.

(b) Effects on delayed matching to position in rats

The effects of Ramelteon (3-30 mg/kg, p.o.), melatonin (10-100 mg/kg, p.o.), diazepam (3-30 mg/kg, p.o.), and triazolam (0.3-3 mg/kg, p.o.) on memory and attention were assessed by delayed matching to position task in rats.[4)] Ramelteon and melatonin at all doses had no effect while diazepam at 30 mg/kg and triazolam at ≥1 mg/kg produced a decrease in the percentage of correct responses.

3.(i).A.(2).2) Effects on endogenous melatonin secretion (Reference data 4.2.1.2-2)

Male rats maintained on a 12-hour lights-on/lights-off cycle (light period from 7:00 to 19:00) were administered Ramelteon (0.3 or 3 mg/kg/day, p.o.) before the dark period (17:30-18:00) once daily for 14 days to examine its effects on endogenous melatonin secretion. There was a trend towards a reduction in plasma melatonin only at one time point (4:00) on the following day of the last dose, which was not statistically significant compared with vehicle.

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

3.(i).A.(3).1) Effects on central nervous system

A single administration of Ramelteon (100 mg/kg, p.o.) to mice resulted in light sedation accompanied by palpebral closure and decreased spontaneous locomotor activity while single administration of Ramelteon (10-100 mg/kg, p.o.) had no significant effect on spontaneous locomotor activity (Reference data 4.2.1.3-6).

A single administration of Ramelteon (10-150 mg/kg, p.o.) to rats had no effect on general symptoms and behavior (4.2.1.3-1).

Following a single administration of Ramelteon (10-100 mg/kg, p.o.) to mice, its anticonvulsant activity was investigated. As a result, maximal electroshock seizures were prevented at 100 mg/kg (Reference data 4.2.1.3-6).

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3) After the last training trial, when the platform was removed from the water tank and the rat was allowed to freely swim, the number of crossings over the former platform location was measured.

4) One of the three lights was illuminated for 5 seconds and after the delay interval (0, 4, 8, or 16 seconds), the three levers were extended into the chamber and the rat was rewarded with food for pressing the lever under the illuminated light.

Following a single administration of Ramelteon (10-100 mg/kg, p.o.) to mice, its analgesic activity was investigated. As a result, Ramelteon had no effect on acetic acid-induced writhing (Reference data 4.2.1.3-6).

Following a single administration of Ramelteon (10-100 mg/kg, p.o.) to rats, its effects on pentobarbital-induced sleeping time were assessed. As a result, Ramelteon, at 100 mg/kg, increased pentobarbital-induced sleeping time (Reference data 4.2.1.3-6).

Following a single administration of Ramelteon (10-100 mg/kg, p.o.) to rats, body temperature was unaffected at all doses (Reference data 4.2.1.3-6).

Following a single administration of Ramelteon (10 mg/kg, p.o.) to cats, its effects on spontaneous EEG were examined. As a result, the drowsiness period[5)] was longer, but no EEG abnormalities were noted (Reference data 4.2.1.3-6).

3.(i).A.(3).2) Pulmonary effects (4.2.1.3-2)

A single administration of Ramelteon (10-150 mg/kg, p.o.) to unanesthetized rats had no effect on respiratory rate, tidal volume, minute ventilation, or enhanced pause (a measure of bronchoconstriction).

3.(i).A.(3).3) Cardiovascular effects

Ramelteon (1-100 μM) or M-II (2*S*, 8*S*) (1-100 μM) had no effect on hERG currents (4.2.1.3-3, 4.2.1.3-4).

The effects of Ramelteon (1-100 μM) on action potential in sheep isolated cardiac Purkinje fibers were investigated. At 100 μM, a shortening of the action potential duration (50.1 ± 9.9% and 39.6 ± 8.6% for APD_{60} and APD_{90}, respectively), a decreased action potential amplitude (-12.8 ± 6.7 mV), and a depolarized resting membrane potential (5.3 ± 3.4 mV) were observed (Reference data 4.2.1.3-7).

A single administration of Ramelteon (66 mg/kg, p.o.) to unanesthetized dogs produced no significant change in heart rate, blood pressure, or electrocardiogram (ECG) (Reference data 4.2.1.3-6).

Following a single administration of Ramelteon (3-50 mg/kg, p.o.) to unanesthetized monkeys, blood pressure (systolic blood pressure, diastolic blood pressure, mean blood pressure), heart rate, and ECG parameters (PR interval, QRS interval, QTc interval) were significantly different from those in the vehicle group, but were similar to the baseline values and were not dose-dependent. Thus, their relationship to Ramelteon was denied (4.2.1.3-5).

5) Drowsiness occurs during wakefulness or at sleep onset and the resting EEG shows a pattern of high amplitude, low frequency, slow waves with spindles.

3.(i).A.(3).4) Effects on autonomic nervous system and smooth muscle (Reference data 4.2.1.3-6)

Ramelteon (10-100 μM) was studied for its antispasmodic activity in isolated guinea pig ileum. Ramelteon at 100 μM slightly inhibited the contractions induced by acetylcholine and histamine, but had no effect on barium-induced contractions.

The effects of Ramelteon (10-100 μM) on the spontaneous motility of isolated rabbit ileum were studied. At 100 μM, a slight inhibition of spontaneous motility was observed.

3.(i).A.(3).5) Renal effects (Reference data 4.2.1.3-6)

A single administration of Ramelteon (10-100 mg/kg, p.o.) to rats had no effect on Na^+ and K^+ excretion or urine volume.

3.(i).A.(3).6) Gastrointestinal effects (Reference data 4.2.1.3-6)

Following a single administration of Ramelteon (10-100 mg/kg, p.o.) to rats, a slight increase in intestinal motility was observed at 100 mg/kg, but there were no effects on gastric emptying at all doses.

3.(i).A.(3).7) Others

Following a single administration of Ramelteon (2-200 mg/kg, p.o.) to monkeys in the morning or evening, decreases in body temperature, heart rate, and activity levels and increased mean blood pressure were observed after the morning administration of Ramelteon 200 mg/kg, and increased mean blood pressure was observed after the evening administration of Ramelteon 200 mg/kg. Following 5-day repeated morning administration of Ramelteon (200 mg/kg/day, p.o.) to monkeys, decreases in body temperature, heart rate, and activity levels and increased mean blood pressure were observed (Reference data 4.2.1.3-8).

Although a single administration of Ramelteon (200 mg/kg, p.o.) to monkeys produced vomiting, pretreatment with either luzindole (a selective MT_2 receptor antagonist, 40 mg/kg, intravenous administration [i.v.]) or granisetron (a 5-HT_3 receptor antagonist, 0.5 mg/kg, i.v.) produced a reduction in both the number of affected monkeys and the number of vomiting episodes, and an increased latency to vomiting. A single administration of melatonin (200 or 1000 mg/kg, p.o.) to monkeys also produced vomiting, but pretreatment with granisetron (0.5 mg/kg, i.v.) reduced the number of affected monkeys and the number of vomiting episodes, and increased the latency to vomiting (Reference data 4.2.1.3-9).

3.(i).A.(4) Pharmacodynamic drug interactions

3.(i).A.(4).1) Effects on diazepam-induced impairment of motor coordination (Reference data 4.2.1.2-3)

In the rota-rod test in mice, the effects of Ramelteon (3-30 mg/kg, p.o.), diazepam (3-10 mg/kg, p.o.), melatonin (3-30 mg/kg, p.o.), and N-acetylserotonin (an agonist for MT_3 binding sites, 3-30 mg/kg, p.o.) on motor coordination were evaluated. Ramelteon, melatonin, or N-acetylserotonin did not impair motor coordination, while diazepam at doses ≥5 mg/kg impaired motor coordination. Although diazepam (3 mg/kg, p.o.) alone did not significantly impair motor coordination, co-administration of diazepam with melatonin (3 and 10 mg/kg, p.o.) or N-acetylserotonin (3 and 10 mg/kg, p.o.) significantly impaired motor

coordination. Co-administration of Ramelteon (3-30 mg/kg, p.o.) with diazepam did not impair motor coordination.

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

3.(i).B.(1) Mechanism of action of Ramelteon

PMDA asked the applicant to explain the mechanism of action of Ramelteon compared with currently marketed hypnotics.

The applicant explained as follows:

In the regulation of the mammalian sleep-wake cycle, sleep-promoting neurons of the ventrolateral preoptic nucleus (ventrolateral preoptic area: VLPO) of the hypothalamus are thought to promote sleep via descending inhibition of the wake-promoting nuclei and the suprachiasmatic nucleus (SCN) is thought to play a central role in the circadian regulation of sleep-wake cycles (Saper CB et al, *Trends Neurosci*, 2001;24: 726-731). As the sleep center VLPO contains GABAergic neurons, it is considered that currently marketed hypnotics, i.e. benzodiazepines ($GABA_A$ receptor agonists) induce sleep by activating GABAergic neurons (Saper CB et al, *Nature*, 2005;473: 1257-1263). However, $GABA_A$ receptors are known to be distributed widely in the brainstem reticular formation, limbic system, hippocampus, cerebellum, spinal cord, cerebral cortex, etc. (Sieghart W et al, *Currr Top Med Chem*, 2002;2: 795-816) and benzodiazepines not only activate GABAergic neurons in the VLPO sleep center but also exert nonspecific inhibitory effects on neurons in other regions of the brain and induce sedated sleep, which is qualitatively different from physiological sleep and causes adverse reactions such as muscle relaxation, anterograde memory impairment, rebound insomnia, and dependence. The SCN has higher neuronal activity in the light period, stimulating the pineal gland via the sympathetic nervous system to promote the synthesis of melatonin and release melatonin during the dark period. It is thought that once released, melatonin binds to the melatonin receptor (primarily MT_1 receptor subtype) in the SCN and inhibits neuronal activity in the SCN, promoting sleep (Dubocovich ML et al, *Front Biosci*, 2003;8: d1093-d1108). It has also been reported that exogenous melatonin phase-shifts circadian rhythms by binding to the MT_2 receptor in the SCN (Liu C et al, *Neuron*, 1997;19: 91-102) etc. Thus, it is considered that Ramelteon contributes to the induction of sleep by selectively activating the MT_1 and MT_2 receptors and modulating the function of the SCN. A distribution study using ^{125}I-2-iodomelatonin, etc. indicate that the MT_1 and MT_2 receptors located in the SCN, thalamus, cerebellum, pituitary gland, retina, etc. are the major sites of action of melatonin (von Gall C et al, *Cell Tissue Res*, 2002;309: 151-162), and these sites of action are specific compared to the distribution of $GABA_A$ receptor α-subunits. As Ramelteon demonstrated no affinity for the $GABA_A$ receptor (4.2.1.1-5), it is considered that Ramelteon has no potential to cause adverse reactions such as muscle relaxation, anterograde memory impairment, rebound insomnia, and dependence.

Considering that differences in the mechanism of action between Ramelteon and currently marketed hypnotics have been discussed appropriately based on the currently available findings, PMDA accepts the above, but considers that it is necessary to determine differences in clinical efficacy between Ramelteon and currently marketed hypnotics based on clinical study data.

3.(i).B.(2) Safety of Ramelteon

Vomiting was observed in a safety pharmacology study in monkeys (Reference data 4.2.1.3-9) and single-dose and repeat-dose toxicity studies in monkeys [see "3.(iii) Summary of toxicology studies"]. PMDA asked the applicant to explain the mechanism of Ramelteon-induced emesis and its clinical safety.

The applicant explained as follows:

In a safety pharmacology study in monkeys (Reference data 4.2.1.3-9), Ramelteon and melatonin at high doses produced vomiting, but pretreatment with luzindole (an MT_2 receptor antagonist) reduced Ramelteon-induced vomiting episodes. Thus, the emetic effect of Ramelteon may have been due to excessive pharmacologic activity of the drug. Meanwhile, since granisetron (a 5-HT_3 receptor antagonist) pretreatment also reduced vomiting episodes induced by Ramelteon or melatonin, it cannot be ruled out that vomiting may be attributed to a non-specific effect, e.g., the involvement of 5-HT_3 receptors in the gastrointestinal tract, and the detailed mechanism of emesis has been undefined. The minimum individual C_{max} and $AUC_{0\text{-}24h}$ of unchanged Ramelteon at the no-observed-effect-level (NOEL) for vomiting (12 mg/kg/day) in 4-week and 39-week repeat-dose toxicity studies in monkeys (4.2.3.2-8 and 4.2.3.2-9) were 31.64 ng/mL and 44.1 ng·h/mL, respectively, and the safety margins relative to the maximum individual C_{max} and $AUC_{0\text{-}24h}$ in Japanese healthy adult subjects (5.3.3.1-2, CPH002) after repeated administration at the clinical dose of 8 mg of Ramelteon (3.23 ng/mL and 4.28 ng·h/mL, respectively) are calculated to be 9.8-fold and 10.3-fold, respectively. When compared with the maximum individual C_{max} and $AUC_{0\text{-}24h}$ estimates[6)] in Japanese healthy elderly subjects (5.3.3.3-1, CPH005) after repeated oral administration at the clinical dose of 8 mg of Ramelteon (18.20 ng/mL and 23.74 ng·h/mL, respectively), the safety margins are calculated to be 1.7-fold and 1.9-fold, respectively. The safety margin of the major metabolite in humans, M-II (2*S*, 8*S*), is unable to be calculated based on these repeat-dose toxicity studies, due to little formation of M-II (2*S*, 8*S*) in monkeys. However, in a 4-week intravenous toxicity study of M-II (2*S*, 8*S*) in monkeys (4.2.3.7.5-2), vomiting did not occur even at the highest dose of 10 mg/kg/day and the minimum individual C_{max} and $AUC_{0\text{-}24h}$ of M-II (2*S*, 8*S*) at 10 mg/kg/day were 6982 ng/mL and 6481 ng·h/mL, respectively, and when compared with the maximum individual C_{max} and $AUC_{0\text{-}24h}$ in Japanese healthy adult subjects (5.3.3.1-2, CPH002) after repeated administration at the clinical dose of 8 mg (66.33 ng/mL and 310.708 ng·h/mL, respectively), the safety margins are calculated to be 105-fold and 22-fold, respectively. When compared with the maximum individual C_{max} and $AUC_{0\text{-}24h}$ estimates[6)] of M-II (2*S*, 8*S*) in Japanese healthy elderly subjects (5.3.3.3-1, CPH005) after repeated oral administration at the recommended clinical dose of 8 mg (82.6 ng/mL and 413 ng·h/mL, respectively), the safety margins are calculated to be 85-fold and 17-fold, respectively. In Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), the incidence of emetic adverse events was 0.7% (11 of 1674 subjects) in the Ramelteon group and 0.2% (2 of 923 subjects) in the placebo group[7)] for nausea and 0.2% (4 of 1674 subjects) in the Ramelteon group and 0% (0 of 923 subjects) in the placebo group for vomiting. There was

6) Estimated from the maximum C_{max} and AUC of unchanged Ramelteon or the metabolite following a single oral dose of 16 mg of Ramelteon in Japanese healthy elderly subjects (5.3.3.3-1, CPH005).

7) Data from 61 subjects during the placebo treatment period in a phase II study (5.3.5.1-1, CCT001) and 380 subjects treated with placebo from Days 1 to 14 in a phase II/III study (5.3.5.1-2.1, CCT002) were used.

no increase in the incidence of emetic adverse events with Ramelteon 8 mg compared to placebo and the reported events were mild or moderate in severity. Thus, nausea, vomiting, etc. associated with Ramelteon are unlikely to become a clinically relevant problem.

There were effects on heart rate and blood pressure in safety pharmacology and general pharmacology studies. PMDA asked the applicant to explain the possibility of these effects in a clinical setting.

The applicant explained as follows:
Cardiovascular effects of Ramelteon observed in a safety pharmacology study were significant compared with vehicle, but the measurements were similar to the baseline values in individual monkeys. In addition, heart rate changes were within the range of diurnal variation, showing no dose-dependence. Thus, these effects are considered to be of little biological significance and unrelated to Ramelteon. These cardiovascular events were only observed at 200 mg of Ramelteon, and the minimum C_{max} and $AUC_{0\text{-}24h}$ at 200 mg were 9765 ng/mL and 17,720 ng·h/mL, respectively. When compared with the maximum individual C_{max} and $AUC_{0\text{-}24h}$ estimates[6)] in Japanese elderly subjects (5.3.3.3-1, CPH005) after repeated administration at the clinical dose of 8 mg (18.20 ng/mL and 23.74 ng·h/mL, respectively), the safety margins are calculated to be 537-fold and 746-fold, respectively. Also in Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), no clinically significant cardiovascular adverse events were reported.

PMDA considers as follows:
In light of blood concentrations etc., nausea and vomiting and cardiovascular effects observed following Ramelteon administration are unlikely to become a particular problem in a clinical setting, but it is necessary to determine the safety of Ramelteon based on clinical study data.

3.(i).B.(3) Tolerance to Ramelteon
PMDA asked the applicant to explain the possibility of the development of tolerance with chronic administration of Ramelteon.

The applicant explained as follows:
Although non-clinical studies in monkeys and cats to characterize the sleep-promoting action of Ramelteon were conducted, the effects of repeated administration on sleep have not been studied, and there is also no report on a repeat-dose non-clinical study with melatonin or a melatonin receptor agonist. As to the desensitization of MT_1 and MT_2 receptors, it has been reported that physiological concentrations (400 pM) of melatonin did not desensitize MT_1 receptors but high concentrations (100 nM) of melatonin desensitized MT_1 receptors (Gerdin MJ et al, *Biochem Pharmacol*, 2004;67: 2023-2030) and that even physiological concentrations of melatonin desensitized MT_2 receptors (Gerdin MJ et al, *FASEB J*, 2004;18: 1646-1656). Thus, the possibility of the development of tolerance due to the desensitization of MT_1 and MT_2 receptors after chronic activation of these receptors by high concentrations of melatonin or a melatonin receptor agonist can not be ruled out. However, after removal of the agonist, the MT_1 and MT_2 receptor functions were restored over time in both studies. Following once daily administration of 8 mg of Ramelteon to

healthy adult subjects, the C_{max} of unchanged Ramelteon in blood on Day 7 was 5.67 nM (5.3.3.1-2, CPH002). Ramelteon demonstrated approximately 6-fold and 4-fold greater affinity for the MT_1 and MT_2 receptors, respectively, than melatonin. Compared with melatonin, Ramelteon demonstrated approximately 4-fold and 17-fold greater potency at the MT_1 and MT_2 receptors, respectively, as measured by the inhibition of cAMP production (4.2.1.1-2, 4.2.1.1-3). Thus, the C_{max} of Ramelteon appears to be equivalent to 20 to 100 nM of melatonin. But, as Ramelteon is eliminated with a half-life of 0.92 to 1.08 hours and becomes undetectable by 12 hours after repeated administration, tolerance is unlikely to develop with once daily administration of the clinical dose of 8 mg of Ramelteon.

PMDA considers that although the discussion based on pharmacologic activity indicates that tolerance is unlikely to develop with administration of the clinical dose of Ramelteon, it is necessary to determine the efficacy of Ramelteon during long-term treatment based on clinical study data.

3.(ii) Summary of pharmacokinetic studies

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

The results from absorption, distribution, metabolism, and excretion studies in rats, dogs, and monkeys were submitted. Plasma concentrations of unchanged Ramelteon and its metabolite (M-II [2-hydroxy metabolite]) were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS) according to validated procedures (Lower limit of quantitation, 0.5 ng/mL [rat plasma] or 0.05 ng/mL [monkey plasma] for unchanged Ramelteon, 0.5 ng/mL for M-II). In studies using ^{14}C-Ramelteon, plasma radioactivity was determined by liquid scintillation counter or high performance liquid chromatography-on-line flow scintillation analyzer (Lower limit of quantitation, [redacted] times the background radioactivity). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation (SD).

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

A single oral or intravenous dose of 1 mg/kg of ^{14}C-Ramelteon was administered to male rats. Following oral administration, total radioactivity in plasma reached C_{max} (0.284 ± 0.003 μg eq./mL) at 0.5 hours post-dose and was eliminated with a $t_{1/2}$ of 40.5 hours. The $AUC_{0\text{-}inf}$ was 2.021 ± 0.079 μg eq.·h/mL. The absorption rate after oral administration calculated from the $AUC_{0\text{-}inf}$ after intravenous administration (2.525 ± 0.096 μg eq.·h/mL) was 80.1% (4.2.2.2-1).

Following a single oral dose of 1 mg/kg of Ramelteon in male rats, plasma concentrations of unchanged Ramelteon reached C_{max} (17.53 ± 8.55 ng/mL) at 0.25 hours post-dose and were eliminated biphasically (α- and β-phase elimination half-lives [$t_{1/2\alpha}$ and $t_{1/2\beta}$] were 0.54 and 7.70 hours, respectively). The $AUC_{0\text{-}inf}$ was 21.30 ± 8.57 ng·h/mL. The $AUC_{0\text{-}inf}$ of unchanged Ramelteon in plasma after intravenous administration was 336.65 ± 30.42 ng·h/mL and the oral bioavailability calculated from the ratio of $AUC_{0\text{-}inf}$ was 6.3% (4.2.2.2-3).

Following a single oral dose of 1 mg/kg of Ramelteon in male dogs, plasma concentrations of unchanged Ramelteon reached C_{max} (112 ± 94.7 ng/mL) at 0.1 hours post-dose and were eliminated biphasically ($t_{1/2\alpha}$

and $t_{1/2\beta}$ were 0.60 and 2.4 hours, respectively). The $AUC_{0\text{-}24h}$ was 129 ± 68.5 ng·h/mL. Plasma concentrations of metabolites (M-II, M-III [6-oxo metabolite], M-IV [2-hydroxy-6-oxo metabolite]) reached C_{max} (168 ± 101, 0.625 ± 0.474, and 10.2 ± 4.52 ng/mL, respectively) at 0.3, 0.3, and 1.0 hours post-dose, respectively and the $AUC_{0\text{-}24h}$ values were 338 ± 148, 0.293 ± 0.284, and 81.0 ± 26.5 ng·h/mL, respectively (4.2.2.2-5).

A single oral or intravenous dose of 0.3 mg/kg of ^{14}C-Ramelteon was administered to male monkeys. Following oral administration, total radioactivity in plasma reached C_{max} (0.238 ± 0.082 μg eq./mL) at 0.31 hours post-dose and was eliminated with a $t_{1/2}$ of 86.34 hours. The $AUC_{0\text{-}inf}$ was 1.492 ± 0.238 μg eq.·h/mL. The absorption rate after oral administration calculated from the $AUC_{0\text{-}inf}$ of plasma radioactivity after intravenous administration (1.931 ± 0.283 μg eq.·h/mL) was 77.7% (4.2.2.2-2).

Following a single oral dose of 0.3 mg/kg of Ramelteon in male monkeys, plasma concentrations of unchanged Ramelteon reached C_{max} (0.525 ± 0.595 ng/mL) at 0.33 hours post-dose and were eliminated with a $t_{1/2}$ of 0.71 hours. The $AUC_{0\text{-}inf}$ was 0.414 ± 0.211 ng·h/mL and the bioavailability calculated from the $AUC_{0\text{-}inf}$ of unchanged Ramelteon in plasma after intravenous administration (169.345 ± 41.003 ng·h/mL) was 0.3% (4.2.2.2-4).

Following single oral doses of 0.03, 0.1, and 0.3 mg/kg of Ramelteon in male monkeys, plasma concentrations of unchanged Ramelteon reached C_{max} (0.050 ± 0.065, 0.271 ± 0.179, and 1.094 ± 1.109 ng/mL, respectively) at 0.3 to 0.4 hours post-dose and the $AUC_{0\text{-}24h}$ values were 0.024 ± 0.035, 0.289 ± 0.183, and 1.033 ± 1.096 ng·h/mL, respectively, indicating a dose-dependent increase (4.2.2.2-6).

Male rats were orally administered 1 mg/kg/day of ^{14}C-Ramelteon once daily for 14 days. The pharmacokinetic parameters of plasma radioactivity were as shown in the following table. Although the C_{max} and $AUC_{0\text{-}24h}$ were increased and the $t_{1/2}$ was prolonged after repeated administration, it appeared that steady state was nearly achieved by Day 7 (4.2.2.2-7).

Table. Pharmacokinetic parameters of plasma radioactivity
following repeated oral administration of 1 mg/kg/day of ^{14}C-Ramelteon once daily for 14 days in rats

	C_{max} (μg eq./mL)	t_{max} (h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$AUC_{0\text{-}24h}$ (μg eq.·h/mL)
Day 1	0.297 ± 0.048	1.00 ± 0.00	1.12 ± 0.30	8.31 ± 0.81	1.492 ± 0.262
Day 7	0.409 ± 0.051	0.50 ± 0.00	1.51 ± 0.08	16.11 ± 4.59	2.018 ± 0.326
Day 14	0.452 ± 0.113	0.50 ± 0.00	1.37 ± 0.28	16.91 ± 1.00	2.201 ± 0.261

When 10 μM of ^{14}C-Ramelteon was added to Caco-2 cells derived from a human colorectal carcinoma, the apparent permeability coefficient (Papp) was similar in the apical (A) to basolateral (B) and basolateral to apical directions and higher than that of highly permeable propranolol. The Papp of Ramelteon was unaffected by the presence of quinidine (a P-glycoprotein inhibitor) (4.2.2.2-8).

Following the administration of 1 mg/kg of ^{14}C-Ramelteon into the ligated pyloric, duodenal, jejunal, ileal, or colonic loop of the male rat, 6.7%, 0.5%, 0.4%, 0.5%, or 18.3%, respectively, of the administered dose remained in the loop at 4 hours after administration, indicating that Ramelteon is absorbed from wide regions of the gastrointestinal tract (4.2.2.2-9).

Following the administration of 1 mg/kg of ^{14}C-Ramelteon into the jejunal loop of the male rat, 90.8% of the administered radioactivity was recovered in portal blood within 2 hours of dosing and most of radioactivity detected in portal plasma was associated with unchanged Ramelteon, indicating that Ramelteon is absorbed almost unchanged into portal circulation (4.2.2.2-10, 4.2.2.2-11).

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

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male rats, tissue radioactivity reached C_{max} at 15 minutes post-dose in most tissues and the tissues with highest concentrations of radioactivity other than the gastrointestinal wall were the liver, kidney, and adrenal gland (in descending order) and radioactivity was distributed into the brain as well. Radioactivity levels were low or below the lower limit of quantitation in many tissues at 48 hours post-dose (4.2.2.3-1).

Male rats were orally administered 1 mg/kg/day of ^{14}C-Ramelteon once daily for 21 days. Tissue radioactivity concentrations were increased by repeated administration, but steady-state was nearly achieved by Day 21. Tissue radioactivity was highest in the liver, followed by the Harderian gland, kidney, and then thyroid gland on Day 21 and gradually disappeared after administration was stopped (4.2.2.3-2).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male and female rats, tissue distribution was determined by whole-body autoradiography. Tissue radioactivity reached C_{max} within 30 minutes post-dose in many tissues, and other than the gastrointestinal tract, the highest radioactivity levels were detected in the liver and kidney. At 48 hours post-dose, radioactivity disappeared from many tissues except the gastrointestinal content and liver and there were no gender differences in tissue distribution of radioactivity (4.2.2.3-3).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male albino rats and male pigmented rats, the radioactivity concentration was about 2-fold higher in the pigmented rat eyeball compared with the albino rat eyeball, but radioactivity disappeared rapidly in pigmented rats as in albino rats and the concentration of remaining radioactivity at 24 hours post-dose was only 4% of the C_{max} value (4.2.2.3-4).

Following a single oral dose of 1 mg/kg of Ramelteon in male rats, plasma and brain concentrations were similar for unchanged Ramelteon and M-II. The great majority of M-II in plasma and brain was of the (2*S*, 8*S*) configuration (4.2.2.3-5, 4.2.2.3-6).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in rats at Day 19 of pregnancy, the fetal plasma contained higher concentrations of radioactivity than the maternal plasma at 0.5 and 2 hours post-dose though after 4 hours of administration, the fetal plasma concentration curve resembled the maternal plasma concentration curve. The fetal tissue, placenta, and amniotic fluid exhibited equivalent or lower radioactivity than the maternal plasma concentrations. While M-III was principally detected in the maternal plasma, the major species in the fetal plasma were unchanged Ramelteon and M-II (4.2.2.3-7, 4.2.2.3-8).

When ^{14}C-Ramelteon was added *in vitro* to rat, dog, and monkey blood to reach final concentrations of 0.01 to 1 μg/mL, the distribution of Ramelteon in blood cells was 25.4% to 27.2%, ≤3.4%, and 23.3% to 26.2%, respectively (4.2.2.3-9).

When ^{14}C-Ramelteon was added *in vitro* to rat, dog, and monkey plasma to reach final concentrations of 0.01 to 1 μg/mL, the plasma protein binding in [redacted] was 85.9% to 86.6%, 92.9% to 96.9%, and 81.2% to 82.0%, respectively (4.2.2.3-10).

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

When ^{14}C-Ramelteon was added *in vitro* to hepatic microsomes from male mice, male and female rats, male dogs, and male monkeys at a final concentration of 50 μM, the main metabolite formed was M-VII ([redacted]) in all animal species and M-II was also a major metabolite in the dog (4.2.2.4-1).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male rats, the M-III, M-I (a ring-opened metabolite), M-II, M-IV, M-VI ([redacted]) metabolites, etc. as well as unchanged Ramelteon were detected in plasma up to 1 hour post-dose (4.2.2.4-2).

Following a single oral dose of 0.3 mg/kg of ^{14}C-Ramelteon in male monkeys, unchanged Ramelteon was not detected and the main metabolite was the M-VII glucuronide in plasma up to 1 hour post-dose (4.2.2.4-3).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male rats, unchanged Ramelteon was not detected in the urine or feces up to 24 hours post-dose, and M-IV and M-I were mainly detected in the urine and feces, respectively (4.2.2.4-4).

Following a single oral dose of 0.3 mg/kg of ^{14}C-Ramelteon in male monkeys, unchanged Ramelteon was not detected in the urine or feces up to 24 hours post-dose, and the M-VII glucuronide was mainly detected in the urine and M-I and M-VII were mainly detected in the feces (4.2.2.4-6).

Following a single intraduodenal administration of 1 mg/kg of ^{14}C-Ramelteon to bile-duct cannulated male rats, M-I was mainly detected and other metabolites such as the M-IX (4-hydroxy metabolite) glucuronide were also found in the bile up to 24 hours post-dose (4.2.2.4-5).

Following administration of ^{14}C-Ramelteon to rats and monkeys, metabolites in biological matrices were isolated and characterized. As a result, the metabolic pathways of Ramelteon have been postulated as shown in the following figure (4.2.2.4-7, 4.2.2.4-9).

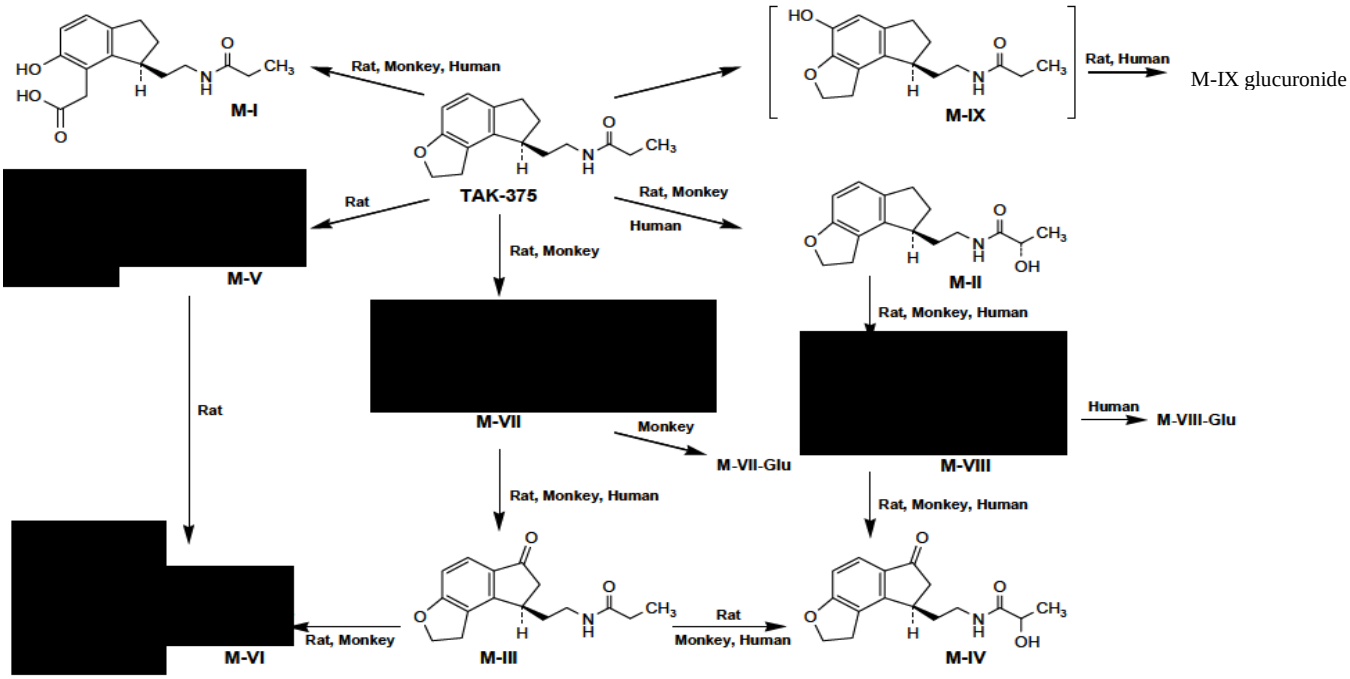

Figure. Postulated metabolic pathways of Ramelteon

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

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in male rats, 59.0%, 31.4%, and 4.8% of the administered radioactivity were excreted in the urine, feces, and expired air, respectively, up to 72 hours post-dose (4.2.2.5-1).

Following a single oral dose of 0.3 mg/kg of ^{14}C-Ramelteon in male monkeys, 77.2% and 11.3% of the administered radioactivity were excreted in the urine and feces, respectively, up to 168 hours post-dose (4.2.2.2-2).

Following a single intraduodenal administration of 1 mg/kg of ^{14}C-Ramelteon to bile-duct cannulated male rats, 36.0% of the administered radioactivity was excreted in the bile up to 24 hours post-dose. When the bile was pooled from an animal receiving 1 mg/kg of ^{14}C-Ramelteon and administered intraduodenally to a separate male rat, 21.1% and 19.2% of the administered radioactivity were excreted in the bile and urine, respectively, up to 24 hours post-dose, indicating enterohepatic circulation of Ramelteon or some of its metabolites (4.2.2.5-2).

Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in rats on Day 14 after parturition, mammary gland tissue and maternal plasma concentrations of radioactivity were equivalent and a 2.4- to 4.8-fold higher concentration was obtained from milk when compared with maternal plasma up to 4 hours post-dose, but milk and maternal plasma concentrations were equivalent at 24 hours post-dose. The major metabolites in milk were M-III and M-IV (4.2.2.5-3, 4.2.2.5-4).

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

3.(ii).B.(1) Accumulation of Ramelteon and safety in humans

As distribution studies revealed high concentrations of radioactivity in the thyroid gland, liver, kidney etc., PMDA asked the applicant to explain the safety of Ramelteon in these organs/tissues during long-term treatment.

The applicant explained as follows:
Rat distribution studies (4.2.2.3-1, 4.2.2.3-2) revealed high concentrations of radioactivity in the thyroid gland, liver, kidney, etc., and analysis was provided for those organs. In rat repeat-dose toxicity (4.2.3.2-3, 4.2.3.2-5, 4.2.3.4.1-5) and carcinogenicity (4.2.3.4.1-6) studies, the thyroid gland findings were increased thyroid gland weight, follicular epithelial cell hypertrophy, low T_3, high TSH, etc. These findings are considered attributed to the induction of hepatic drug-metabolizing enzymes producing increased thyroid hormone glucuoronidation and subsequent excretion of thyroid hormone, which leads to increased TSH secretion from the pituitary gland through a negative feedback mechanism. In the liver, changes suggestive of liver injury, e.g. necrosis of hepatocytes, were observed at a high dose (250 mg/kg/day) in the rat carcinogenicity study (4.2.3.4.1-6), but these events did not occur in other repeat-dose toxicity studies (26 weeks for rats, 39 weeks for monkeys). In the kidney, findings suggestive of kidney injury, e.g. an increased incidence or severity of basophilic renal tubules, were observed in males at ≥150 mg/kg/day and females at 1200 mg/kg/day in a rat 13-week dose range-finding toxicity study (4.2.3.4.1-5), but all of these events occurred at doses extremely higher than the human dose. In Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), the main adverse events affecting these organs/ tissues with a higher incidence in the Ramelteon group than in the placebo group[7)] were blood triglycerides increased (0.8% [7 of 923 subjects] in the placebo group, 1.4% [23 of 1674 subjects] in the Ramelteon group) etc., but the observed events were mild or moderate in severity and there was no trend towards an increased incidence with prolonged treatment. Therefore, a safety problem is unlikely to occur in these organs/tissues in a clinical setting.

As the melanin affinity of Ramelteon was suggested (4.2.2.3-4), PMDA asked the applicant to explain the safety of Ramelteon in melanin-containing tissues (skin and eyeball, etc.).

The applicant explained as follows:
Following a single oral dose of 1 mg/kg of ^{14}C-Ramelteon in pigmented rats, the pigmented rat eyeball concentration of radioactivity was higher than the albino rat eyeball concentration (4.2.2.3-4), but radioactivity disappeared rapidly in pigmented rats as in albino rats. Therefore, it is considered that Ramelteon or its metabolites does not show high affinity for melanin-containing tissues. Based on the results of this study, a simulation of eyeball concentrations, following once-daily repeated oral administration of 1 mg/kg of Ramelteon, was performed, which indicated that steady state would be reached within 4 weeks. Thus, there will be no significant tissue accumulation. In toxicity studies in pigmented animals, i.e. mice and monkeys, ocular toxicity or skin toxicity was not noted. In Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), the incidence of adverse events classified as eye disorders or skin and subcutaneous tissue disorders was slightly higher in the Ramelteon group than in the placebo group[7)] (eye disorders, 0.4% [4 of 923 subjects] in the placebo group, 0.7% [12 of 1674 subjects] in the Ramelteon group; skin and subcutaneous tissue

disorders, 0.7% [6 of 923 subjects] in the placebo group, 1.9% [31 of 1674 subjects] in the Ramelteon group), but the observed events were all mild or moderate in severity and there was no trend towards an increased incidence with prolonged treatment. Therefore, there should be no major problem with the safety of Ramelteon in melanin-containing tissues.

PMDA considers that there is no major problem with the safety of Ramelteon in the organs/tissues where high concentrations of radioactivity were detected in distribution studies (thyroid gland, liver, kidney, etc.) or in melanin-containing tissues, but it is necessary to continue to investigate the safety of Ramelteon in these organs/tissues via post-marketing surveillance.

3.(iii) Summary of toxicology studies

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

Toxicity studies of Ramelteon conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity (dependence, toxicity of a metabolite and impurities) studies. PMDA considered that some of the dependence studies were GLP non-compliant, but can be evaluated as reference data.

3.(iii).A.(1) Single-dose toxicity

Oral and intravenous single dose toxicity studies in rats and an oral escalating dose toxicity study in monkeys were conducted.

3.(iii).A.(1).1) Oral administration study in rats (4.2.3.1-1)

Following single oral doses of 200, 600, or 2000 mg/kg of Ramelteon in rats (5 rats/sex/group), one female in the 2000 mg/kg group exhibited bradypnea, lying on side, lacrimation, salivation, and twitches and was found dead the next morning. In surviving rats, decreased touch-escape response and ataxic gait at ≥600 mg/kg and decreased body weight gain, decreased spontaneous motor activity, prone position, and decreased body temperature at 2000 mg/kg were observed. Necropsy of the dead rat revealed red scattered spots in the lungs and stomach, distended stomach with white liquid, and enlarged adrenals. Based on the above, the approximate lethal dose was determined to be ≥2000 mg/kg for males and between 600 and 2000 mg/kg for females.

3.(iii).A.(1).2) Oral administration study in monkeys (4.2.3.1-4)

Following oral escalating doses of 2, 20, 200, and 2000 mg/kg of Ramelteon separated by 3- or 4-day washout periods in monkeys (2 males and 2 females), decreased body temperature and decreased heart rate at ≥20 mg/kg, vomiting at ≥200 mg/kg, and salivation and pale oral mucosa at 2000 mg/kg were observed, but no death occurred. Thus, the approximate lethal dose was determined to be >2000 mg/kg for both males and females. It has been reported that melatonin induces decreased body temperature and decreased heart rate (Krauchi K et al, *Am J Physiol*, 1997;272: 1178-1188). The decreased body temperature and decreased heart rate are considered a pharmacologic extension of Ramelteon.

3.(iii).A.(1).3) Intravenous administration study in rats

Following single intravenous doses of 6, 20, or 60 mg/kg of Ramelteon in rats (5 rats/sex/group), 3 males in the 60 mg/kg group died within 1 minute after injection. In surviving animals, decreased spontaneous motor activity, decreased touch-escape response, prone or lateral position, ataxic gait, bradypnea, and pale skin at all dose levels of Ramelteon, and hypothermia at 60 mg/kg were observed. Based on the above, the approximate lethal dose was determined to be between 20 and 60 mg/kg for males and ≥60 mg/kg for females (4.2.3.1-2).

Following single intravenous doses of 0.02, 0.2, or 2 mg/kg of Ramelteon in rats (5 rats/sex/group), no deaths or toxicological findings were observed at any dose level. Therefore, the approximate lethal dose was determined to be >2 mg/kg for both males and females (4.2.3.1-3).

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

Oral repeat-dose toxicity studies in rats (4 and 26 weeks) and monkeys (4 and 39 weeks) were conducted. The major toxicological findings included vacuolization of the cortical cells of the adrenal gland and interstitial cells in the ovary and anemia in the rat, and vomiting and elevated ALT (GPT) in the monkey. These effects were reversible. Effects in the liver associated with the induction of drug metabolizing enzymes (increased liver weight and hepatocellular hypertrophy) were also noted. The no-observed-adverse-effect level (NOAEL) was determined to be 10 mg/kg/day in the rat and 12 mg/kg/day in the monkey, regardless of the duration of dosing. When the exposure ($AUC_{0\text{-}24h}$[8)]) of unchanged Ramelteon or metabolites at the NOAEL was compared with the human exposure at the clinical dose of 8 mg, the safety margin was ≥150-fold in all animal species for unchanged Ramelteon, M-I, and M-III, while the safety margin was >5-fold in the rat and <1-fold in the monkey for M-II and M-IV. The results of a separate 4-week intravenous toxicity study of M-II in monkeys (4.2.3.7.5-2) indicated that there is no toxicological concern for M-II [see "3.(iii).A.(7).2) Toxicity studies on metabolite"]. Although the M-IV exposure at the lowest observed adverse effect level (50 mg/kg/day) in the monkey 39-week oral administration study (4.2.3.2-9) was about 8-fold the human exposure at the clinical dose, the toxicological finding observed at this dose level was vomiting in 1 animal only, and M-IV is not pharmacologically active (4.2.1.1-3). Therefore, M-IV is also considered of little toxicological concern.

8) The $AUC_{0\text{-}24h}$ values of unchanged Ramelteon and metabolites at 8 mg were estimated (unchanged Ramelteon, 9.2 ng·h/mL; M-I, 7.7 ng·h/mL; M-II, 259.2 ng·h/mL; M-III, 2.7 ng·h/mL; M-IV, 53.0 ng·h/mL) from the $AUC_{0\text{-}24h}$ values of unchanged Ramelteon and metabolites in Japanese healthy elderly subjects following a single oral dose of 16 mg of Ramelteon (5.3.3.3-1, CPH005).

3.(iii).A.(2).1) Rat 4-week oral administration study (4.2.3.2-3)

Following 4-week oral administration of 10, 40, 150, or 600 mg/kg/day of Ramelteon to rats (10 rats/sex/group), no death occurred and an increase in plasma total cholesterol, increased thyroid weight, and adrenal cortical vacuolization at ≥40 mg/kg/day, salivation, increased adrenal gland weight, dark discolored liver, hepatocellular hypertrophy, enlarged adrenals, and vacuolization of ovarian interstitial cells at ≥ 150 mg/kg/day, and decreased body weight gain, decreased food intake, chromaturia, increases in plasma total protein, Ca, and triglycerides, increased liver weight, and enlarged liver at 600 mg/kg/day were observed. As for thyroid and thyroid-stimulating hormones, T_3 levels were reduced at ≥150 mg/kg/day (females) and T_4 levels were increased (males) and TSH levels were decreased (males) or increased (females) at 600 mg/kg/day. As for hepatic drug-metabolizing enzymes, the activity of aniline hydroxylase was increased at ≥150 mg/kg/day and the activity of aminopyrine N-demethylase was increased and T_4 and 4-nitrophenol glucuronidation activities were also increased at 600 mg/kg/day. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).2) Rat 4-week oral administration study with a 13-week recovery period (4.2.3.2-4)

Following 4-week oral administration of 600 mg/kg/day of Ramelteon to rats (30 rats/sex/group), no death occurred. At the end of dosing, decreased body weight gain, decreased food intake, salivation, chromaturia, increases in plasma triglycerides, total cholesterol, and total protein, increased adrenal gland weight, enlarged adrenal gland, adrenal cortical vacuolization, increased liver weight, enlarged liver, dark discolored liver, hepatocellular hypertrophy, intracytoplasmic inclusion bodies in the liver, vacuolization of ovarian interstitial cells, decreased T_3 levels (males and females), and increased TSH levels (females) were observed. In the recovery period, chromaturia was observed during the 1st week of recovery, and an increase in plasma total protein, increased liver weight, and adrenal cortical vacuolization persisted at 4 weeks of recovery, but there were no findings by the end of 13-week recovery. Therefore, it is considered that the changes associated with 4-week dosing of Ramelteon are all reversible and recoverable.

3.(iii).A.(2).3) Rat 26-week oral administration study (4.2.3.2-5)

Following 26-week oral administration of 2.5, 10, 40, or 150 mg/kg/day of Ramelteon to rats (15 rats/sex/group), no death occurred. At ≥40 mg/kg/day, salivation, increased thyroid weight, hepatocellular hypertrophy, and adrenal cortical vacuolization were observed. At 150 mg/kg/day, increased food consumption (during the last week of dosing); decreases in erythrocyte count and hematocrit and hemoglobin levels; increases in plasma total protein and total cholesterol; increased weights of the liver, kidney, spleen, and adrenal gland; dark and enlarged livers; thyroid follicular cell hypertrophy; vacuolization of ovarian interstitial cells; extramedullary hematopoiesis and brown pigmentation of the spleen; a reduction in T_3 (females); and an increase in TSH (females) were observed. There were no changes in the activities of hepatic drug-metabolizing enzymes (aniline hydroxylase, aminopyrine-N-demethylase). Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).4) Monkey 4-week oral administration study (4.2.3.2-8)

Following 4-week oral administration of 3, 12, 50, or 200 mg/kg/day of Ramelteon to monkeys (3 monkeys/sex/group), no death occurred, and decreased body temperature and decreased heart rate at ≥12

mg/kg/day, vomiting at ≥50 mg/kg/day, and increased platelet count, elevated ALT (GPT), and increased liver weight at 200 mg/kg/day were observed. As for hepatic drug-metabolizing enzymes, the activity of aminopyrine-N-demethylase was increased at ≥12 mg/kg/day and the activity of aniline hydroxylase was increased at ≥50 mg/kg/day. There were no changes in plasma T_3 or T_4 levels. As decreased body temperature and decreased heart rate observed at ≥12 mg/kg/day are considered a pharmacologic extension of Ramelteon [see "3.(iii).A.(1) Single-dose toxicity"], the NOAEL was determined to be 12 mg/kg/day.

3.(iii).A.(2).5) Monkey 39-week oral administration study (4.2.3.2-9)

Following 39-week oral administration of 3, 12, 50, or 200 mg/kg/day of Ramelteon to monkeys (4 monkeys/sex/group), no death occurred and vomiting at ≥50 mg/kg/day and increases in plasma ALT (GPT) and triglycerides, increased liver weight, and hepatocellular hypertrophy at 200 mg/kg/day were observed. There were no changes in the activities of hepatic drug-metabolizing enzymes (aniline hydroxylase, aminopyrine-N-demethylase). Based on the above, the NOAEL was determined to be 12 mg/kg/day.

3.(iii).A.(3) Genotoxicity

As genotoxicity studies, a bacterial reverse mutation assay (4.2.3.3.1-1), an *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells (4.2.3.3.1-3), a gene mutation assay using the mouse lymphoma L5178Y (TK+/−) cell line (4.2.3.3.1-5), oral bone marrow micronucleus assays in the mouse and rat (4.2.3.3.2-1, 4.2.3.3.2-2), and an *in vivo*/*in vitro* unscheduled DNA synthesis (UDS) assay in rat hepatocytes (4.2.3.3.2-3) were performed. Although there was an increase in chromosomal aberrations considered related to cytotoxicity in the chromosomal aberration assay, the other assays all produced negative results. Thus, it has been concluded that Ramelteon has no genotoxic potential. The concentrations of Ramelteon metabolites in the reaction mixture for the *in vitro* assays with S9 mix metabolic activation were measured, which demonstrated assay exposure to adequate concentrations of all metabolites as well (Reference data 4.2.3.3.1-2, Reference data 4.2.3.3.1-4, Reference data 4.2.3.3.1-6).

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

Two-year carcinogenicity studies in mice and rats were performed. Hepatic tumors were observed in both animal species and the incidence of Harderian gland adenoma in mice and the incidence of benign Leydig cell tumors of the testis in rats were increased. However, both tumors have little relevance to humans based on their mechanism of development and are not considered suggestive of human risk. When the exposure ($AUC_{0\text{-}24h}$) at the NOEL for hepatic tumors (30 mg/kg/day in mice, 15 mg/kg/day in rats) was compared to the human exposure ($AUC_{0\text{-}24h}$[8)]) at the clinical dose of 8 mg, the safety margin was about 100-fold for unchanged Ramelteon and about 2-fold for M-II and the exposures to other metabolites also exceeded the human exposure at the clinical dose.

3.(iii).A.(4).1) Mouse carcinogenicity study (4.2.3.4.1-3)

Mice (55 mice/sex/group) were orally administered Ramelteon at doses of 30, 100, 300, or 1000

mg/kg/day[9] for 24 months. As for neoplastic lesions, increased incidences of hepatocellular adenoma (males, 20 mice in the negative control group, 24 mice in the Ramelteon 30 mg/kg/day group, 32 mice in the Ramelteon 100 mg/kg/day group, 50 mice in the Ramelteon 300 mg/kg/day group, and 54 mice in the Ramelteon 1000 mg/kg/day group; females, 10 mice, 14 mice, 14 mice, 52 mice, and 55 mice, respectively), hepatocellular carcinoma (males, 9 mice, 6 mice, 18 mice, 26 mice, and 50 mice, respectively; females, 4 mice, 3 mice, 3 mice, 11 mice, and 51 mice, respectively), and hepatoblastoma (males, 0 mice, 0 mice, 1 mouse, 3 mice, and 10 mice, respectively; females, 0 mice, 0 mice, 0 mice, 1 mouse, and 3 mice, respectively) were observed in males at ≥100 mg/kg/day and females at ≥300 mg/kg/day. The incidence of Harderian gland adenoma (males, 6 mice, 15 mice, 14 mice, 16 mice, and 11 mice, respectively; females, 3 mice, 3 mice, 10 mice, 10 mice, and 9 mice, respectively) was increased in males at all dose levels of Ramelteon and females at ≥100 mg/kg/day.

The main non-neoplastic findings possibly related to Ramelteon included centrilobular/periportal hepatocellular hypertrophy, single cell necrosis of hepatocytes, focal necrosis of hepatocytes, and pigmentation of sinusoidal lining cells in the liver; hypertrophy and pigmentation of thyroid follicular epithelial cells; adrenal cortical diffuse hypertrophy; ovarian, uterine, and vaginal atrophy; atrophy of the seminal vesicle; glomerulosclerosis and pigmentation of tubular epithelial cells in the kidney; increased extramedullary hematopoiesis in the spleen; focal squamous cell hyperplasia of the forestomach with inflammatory cell infiltration; erosion of the glandular stomach; and lymphocytic cell infiltration of the epididymis.

3.(iii).A.(4).2) Rat carcinogenicity study (4.2.3.4.1-6)

Rats (60 rats/sex/group) were orally administered Ramelteon at doses of 15, 60, 250, or 1000 mg/kg/day[10] for 24 months. As for neoplastic lesions, the incidence of hepatocellular adenoma (males, 0 rats in the negative control I group, 3 rats in the negative control II group, 7 rats in the Ramelteon 15 mg/kg/day group, 7 rats in the Ramelteon 60 mg/kg/day group, 15 rats in the Ramelteon 250 mg/kg/day group, and 47 rats in the Ramelteon 1000 mg/kg/day group; females, 1 rat, 1 rat, 0 rats, 8 rats, 22 rats, and 49 rats, respectively) was increased in males at ≥15 mg/kg/day and females at ≥60 mg/kg/day and the incidence of hepatocellular carcinoma (males, 0 rats, 0 rats, 0 rats, 0 rats, 0 rats, and 38 rats, respectively; females, 0 rats, 0 rats, 0 rats, 1 rat, 1 rat, and 20 rats, respectively) was increased in males and females at 1000 mg/kg/day. The incidence of benign Leydig cell tumors of the testis was increased in males at ≥250 mg/kg/day (3 rats, 0 rats, 1 rat, 0 rats, 7 rats, and 46 rats, respectively). When the incidence of hepatocellular adenoma in males at 15 or 60 mg/kg/day was compared with one of the two control groups, no statistically significant difference was observed and at 15 mg/kg/day, the increase in the incidence of centrilobular hepatocellular hypertrophy or altered hepatocyte focus was also slight. Therefore, the NOEL for hepatic tumors was determined to be 60 mg/kg/day (males) and 15 mg/kg/day (females). Also for the incidence of Leydig cell tumors of the testis in the 250 mg/kg/day group, no statistically significant difference was noted compared

[9] As the survival rate in the 1000 mg/kg/day group was reduced due to hepatic tumors, this dose group was terminated at Week 94 and the surviving animals were necropsied at Week 95.

[10] As the survival rate was reduced due to toxicity and hepatic tumors in females in the 1000 mg/kg/day group, the surviving animals were necropsied at Week 94.

with one of the two control groups.

The main non-neoplastic findings possibly related to Ramelteon included centrilobular hepatocellular hypertrophy, altered cell focus, spongiosis hepatis, focal necrosis, cystic hyperplasia of the bile duct cells, and proliferation of oval cells in the liver; focal hyperplasia of follicular epithelial cells and increased small follicles in the thyroid; vacuolization and diffuse hypertrophy of adrenal cortical cells; atrophy of the prostate gland, seminal vesicle, and epididymis; focal hyperplasia of the Leydig cells and seminiferous tubular atrophy of the testis; alveolar pigmented histiocytosis in the lung; cerebral mineralization; atrophy of trabecular bone in the femur; and retinal atrophy in the eye and pigmentation was observed in various organs.

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

As reproductive and developmental toxicity studies, rat studies of fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, and a rat study for effects on pre- and postnatal development including maternal function were conducted. In rats, irregularity in the estrous cycles and reductions in the numbers of corpora lutea and implantations in the dams, a decreased survival rate and delayed physical development in the offspring, and an increased fetal mortality and fetal external (cysts on the external genitalia), visceral (diaphragmatic hernia), and skeletal (irregularly shaped scapula and lumbar ribs) abnormalities were observed. When the exposure at the NOAEL for embryo-fetal toxicity was compared with the human exposure ($AUC_{0\text{-}24h}$[8)]) at the clinical dose of 8 mg, the safety margin was ≥1400-fold for unchanged Ramelteon and ≥38-fold for M-II. No teratogenic effects were observed in rabbits. In rats, Ramelteon crossed the placenta into the fetus (4.2.2.3-7) and was excreted into milk (4.2.2.5-3) [see "3.(ii).A.(2) Distribution and 3.(ii).A.(4) Excretion"].

3.(iii).A.(5).1) Rat studies of fertility and early embryonic development to implantation

Rats (20 rats/sex/group) were orally administered Ramelteon at doses of 6, 60, or 600 mg/kg/day. Males were dosed from 4 weeks prior to mating until the day before necropsy (about 10 weeks) and females were dosed from 2 weeks prior to mating until gestation day 6. Salivation in males and irregular estrous cycles in females at ≥60 mg/kg/day, creeping, crouching, lying on side, decreased spontaneous motor activity, ataxic gait, chromaturia, reduced body weight gain, and increased weights of the liver and adrenal gland in males and females at 600 mg/kg/day, decreased food consumption (after the first dose only) and enlarged and dark livers in males at 600 mg/kg/day, and mortality (9 deaths), salivation, decreased food consumption throughout the dosing period, petechia in the stomach, enlarged adrenals, spleen discoloration, and congested lungs in females at 600 mg/kg/day were observed. When treated male rats were mated with treated female rats, there were a decreased number of corpora lutea and associated decreased numbers of implantations and live conceptuses at 600 mg/kg/day. Meanwhile, when the same treated male rats were mated with untreated female rats, there was no effect. Based on the above, the NOAEL was determined to be 60 mg/kg/day for male general toxicity, 600 mg/kg/day for male reproductive toxicity, 6 mg/kg/day for female general and reproductive toxicity, and 600 mg/kg/day for embryonic development (4.2.3.5.1-1).

Since the number of implantations tended to decrease and the incidence of pre- and post-implantation

losses increased or tended to increase at 60 mg/kg/day of Ramelteon in the above study (4.2.3.5.1-1), rats (20 rats/sex/group) were orally administered Ramelteon at doses of 20, 60, or 200 mg/kg/day to determine their relationship to Ramelteon. Males were dosed from 4 weeks prior to mating until the day before necropsy (about 7 weeks) and females were dosed from 2 weeks prior to mating until gestation day 6. As a result, irregular estrous cycles in females at ≥60 mg/kg/day, salivation, creeping, crouching, hypoactivity, and ataxic gait in males and females at 200 mg/kg/day, and decreased body weight gain during gestation and reduced feces in females at 200 mg/kg/day were observed. When treated males were mated with treated females, there was no effect on the number of corpora lutea, implantations, or live conceptuses at all dose levels of Ramelteon. Based on the above, the NOAEL was determined to be 60 mg/kg/day for male general toxicity, 200 mg/kg/day for male reproductive toxicity, 20 mg/kg/day for female general and reproductive toxicity, and 200 mg/kg/day for embryonic development (4.2.3.5.1-3).

Based on the above study results, the NOAEL in the rat studies of fertility and early embryonic development to implantation was determined to be 60 mg/kg/day for males, 20 mg/kg/day for females, and 600 mg/kg/day for embryo.

3.(iii).A.(5).2) Embryo-fetal development studies

(a) Rat study (4.2.3.5.2-2)

Pregnant rats (n = 16-20/group) were orally administered Ramelteon at doses of 10, 40, 150, or 600 mg/kg/day from gestation day 6 to 17. In the dam, salivation, reduced body weight gain, and increased liver weight at ≥150 mg/kg/day and mortality (1 death), total resorption of litter (1 rat), decreased food consumption, lying on one side, reduced spontaneous motor activity, ataxic gait, reduced feces production, increased weight and enlargement of the adrenal gland, and a decrease in the weight of the carcass at 600 mg/kg/day were observed. In the fetus and placenta, the number of live fetuses tended to decrease, the incidence of post-implantation losses tended to increase, and fetal body weight was decreased at 600 mg/kg/day and the incidence of visceral abnormalities (diaphragmatic hernia) was increased at ≥150 mg/kg/day and the incidences of external abnormalities (cysts on the external genitalia) and skeletal variations (irregularly shaped scapula and lumbar ribs) were increased at 600 mg/kg/day. Based on the above, the NOAEL was determined to be 40 mg/kg/day for both maternal toxicity and embryo-fetal toxicity.

(b) Rabbit study (4.2.3.5.2-5)

Pregnant rabbits (n = 18-20/group) were orally administered Ramelteon at doses of 12, 60, or 300 mg/kg/day from gestation day 6 to 18. In the dam, abortions (2 rabbits) and decreased spontaneous motor activity, creeping, lying on one side, muscle rigidity, convulsions, miosis, reduced feces, reduced body weight gain, and decreased food consumption were observed at 300 mg/kg/day. However, there were no effects of Ramelteon on the fetus or placenta. One dam in the 60 mg/kg/day group aborted, but exhibited no abnormalities in clinical observation or the time course of body weight, and the laboratory's historical data indicate that it was a coincidental occurrence. Based on the above, the material NOAEL was determined to be 60 mg/kg/day and the embryo-fetal NOAEL was determined to be 300 mg/kg/day.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-2)

Pregnant rats (n = 19-20/group) were orally administered Ramelteon at doses of 30, 100, or 300 mg/kg/day from Day 6 of pregnancy to Day 21 of lactation. In the dam, reduced body weight gain, reduced food consumption, and increased adrenal gland weight at ≥100 mg/kg/day, and decreased spontaneous motor activity and the loss of all offspring (3 litters) at 300 mg/kg/day were observed. In the offspring, reduced body weight during weaning and at 77 days after birth at ≥100 mg/kg/day and a trend towards a reduction in postnatal survival to Day 4, a delay in incisor eruption and righting reflex, and prolonged latency to ambulation in the open field test at 300 mg/kg/day were observed. Postmortem examination of offspring at weaning revealed diaphragmatic hernia at 300 mg/kg/day. Based on the above, the NOAEL was determined to be 30 mg/kg/day for maternal general toxicity, 100 mg/kg/day for maternal reproductive toxicity, and 30 mg/kg/day for offspring.

3.(iii).A.(6) Local tolerance

An *in vitro* hemocompatibility study, an intravenous local tolerance study in the rabbit, and a paravenous local tolerance study in the rabbit were conducted. Intravenous or paravenous injection of Ramelteon caused slight local irritation, but the irritation was reversible. Ramelteon did not cause hemolysis of human blood *in vitro* and was considered compatible with plasma as well.

3.(iii).A.(6).1) *In vitro* hemocompatibility study using human blood (4.2.3.6-1)

When a 1 mg/mL solution of Ramelteon (dissolved in a 30 w/v % PEG400 solution) was incubated with human blood at a 1:10 ratio at 37°C for 1 minute, no hemolysis occurred. When the same solution was incubated with human plasma at a 1:100 ratio at 37°C for 1 minute, no flocculation, precipitation, or coagulation was observed, and Ramelteon was considered compatible with plasma as well.

3.(iii).A.(6).2) Intravenous local tolerance study in the rabbit (4.2.3.6-2)

In male rabbits (n = 3/group), 3 mL of a 1 mg/mL solution of Ramelteon (dissolved in a 30 w/v % PEG400 solution) was infused into the posterior auricular vein at a rate of 1 mL/minute (3 minutes). Slight erythema at the infusion site was noted on Day 1 after infusion, but resolved on the following day. Histopathological examination of the infusion sites 2 days after infusion revealed slight edema and mononuclear cell infiltration, but no abnormalities were noted 14 days after infusion. Although these changes were not observed in the saline control group, similar gross and histological changes were observed also in the vehicle-treated group. Therefore, it is concluded that a 1 mg/mL solution of Ramelteon (dissolved in a 30 w/v% PEG400 solution) causes a slightly greater local irritation at the site of intravenous infusion than saline, but the irritation is slight and reversible.

3.(iii).A.(6).3) Paravenous local tolerance study in the rabbit (4.2.3.6-3)

In male rabbits (n = 3/group), 0.3 mL of a 1 mg/mL solution of Ramelteon (dissolved in a 30 w/v % PEG400 solution) was injected subcutaneously around the posterior auricular vein. Slight or mild erythema and slight swelling at the injection site were noted on Day 1 after injection, and slight or mild hemorrhage and slight swelling were noted at necropsy 2 days after injection, but no abnormalities were noted 14 days after injection. Histopathological examination of the injection sites 2 days after injection revealed slight or moderate edema and mononuclear cell infiltration, slight or mild hemorrhage, and slight inflammatory cell infiltration, but no abnormalities were noted 14 days after injection. Although these changes were not observed in the saline control group, similar changes were observed in the vehicle-treated group. Therefore, it is concluded that a 1 mg/mL solution of Ramelteon (dissolved in a 30 w/v % PEG400 solution) causes a slightly greater local irritation at the site of paravenous injection than saline, but the irritation is slight and reversible.

(7) Other toxicity studies

Other toxicity studies conducted include dependence studies and toxicity studies on a metabolite and impurities. There was no evidence of physical or psychological dependence in physical dependence studies in rats and monkeys, a conditioned place preference study in rats, and self-administration and drug discrimination studies in monkeys. Since the major metabolite of Ramelteon in humans is M-II (2*S*, 8*S*), the metabolite was qualified in a 4-week intravenous toxicity study in monkeys and an embryo-fetal developmental toxicity study in rats. Although the levels of all impurities specified for Ramelteon are ≤0.15%, which is below the qualification threshold, impurities may have been present in the drug substance at a level greater than the threshold in the early phase of development. Thus, toxicity studies of U-5 (unidentified) and U-6 ([redacted] of Ramelteon) were conducted, and then U-5 and U-6 were qualified.

3.(iii).A.(7).1) Dependence

(a) Physical dependence study in rats (4.2.3.7.4-1)

Male rats (n = 10/group) were fed Ramelteon at 200 or 600 mg/kg/day or diazepam at 300 mg/kg/day in their diet for 4 weeks and then the drug-containing diet was replaced by the control diet. Whereas a withdrawal syndrome (decreased body weight, decreased food intake, irritability, reduced feces) was observed in the diazepam group, these symptoms did not occur in the Ramelteon group. Therefore, Ramelteon is considered to produce no physical dependence in rats.

(b) Physical dependence study in monkeys (Reference data 4.2.3.7.4-2)

Monkeys (3 males and 1 female) were trained to make an operant response under a two-lever compound FR schedule[11)] and intragastrically administered 10 mg/kg/day of Ramelteon for 1 year and the treatment was temporarily discontinued for 5 days during Weeks 14, 27, 40, and 53. No abnormalities in body weight, operant response, or clinical signs were observed throughout the periods of treatment, or after discontinuation of treatment, and no withdrawal syndrome was noted. Therefore, Ramelteon is considered

11) Monkeys were trained to press a lever 10 times when one light was illuminated in order to obtain food reward and press the same lever 10 times when another light was illuminated in order to avoid electroconvulsive shock.

to produce no physical dependence in monkeys.

(c) Conditioned place preference study in rats (Reference data 4.2.3.7.4-3)

In a conditioned place preference study,[12] oral administration of Ramelteon at doses of 3, 10, or 30 mg/kg or melatonin at doses of 10, 30, or 100 mg/kg to male rats (n = 8-11/group) did not increase the time spent in the drug-associated compartment and Ramelteon or melatonin did not exhibit a reinforcing effect. The positive controls, morphine (1 mg/kg), diazepam (5 mg/kg), and triazolam (0.5 mg/kg) were associated with significant increases in the time spent in the drug-associated compartment.

(d) Self-administration study in monkeys (4.2.3.7.4-5)

A single intravenous dose of 1 or 2 mg/kg of Ramelteon was administered to monkeys (3 males and 1 female). As a result, there was no behavioral effect in any animal and Ramelteon produced no acute central nervous system effects.

Monkeys (2 males and 2 females) were free to self-administer intravenous Ramelteon at doses of 0.025, 0.05, 0.1, 0.2, or 0.4 mg/kg/infusion or pentobarbital at doses of 0.125, 0.25, 0.5, or 1.0 mg/kg/infusion over a 2-hour daily session. The number of self-administrations increased in the pentobarbital group but not in the Ramelteon group, and Ramelteon showed no reinforcing effect.

Monkeys (2 males and 2 females) were free to self-administer intravenous Ramelteon at doses of 0.025, 0.1, or 0.4 mg/kg/infusion around the clock. The number of self-administrations did not increase and Ramelteon showed no reinforcing effect.

(e) Drug discrimination studies in monkeys (Reference data 4.2.3.7.4-6 , 4.2.3.7.4-7)

Female monkeys (n = 4), trained to discriminate between midazolam and vehicle, were intravenously administered Ramelteon at doses of 0.32, 1.0, 3.2, 5.6, or 10 mg/kg. Ramelteon at all doses produced no midazolam-like discriminative stimulus effects.

Monkeys (3 males and 1 female) dependent on diazepam were trained to discriminate a flumazenil (a benzodiazepine receptor antagonist, 3.2-320 μg/kg, s.c.)-induced withdrawal syndrome, and were intravenously administered Ramelteon at doses of 1, 3.2, 5.6, or 10 mg/kg 15 minutes prior to the administration of flumazenil. Ramelteon did not attenuate the discriminative stimulus effects of flumazenil, indicating that Ramelteon does not have benzodiazepine-like effects.

[12] Before drug administration, animals were placed in a 2-compartment box (white and black) and were allowed to move freely between the compartments and the time spent in each compartment was measured (Phase I). The animals were administered drug on Days 1 and 3 and confined to the non-preferred compartment and administered saline on Days 2 and 4 and confined to the preferred compartment (Phase II). Then, the animals were allowed to move freely between the compartments again (Phase III) and the time spent in each compartment was measured.

3.(iii).A.(7).2) Toxicity studies on metabolite

(a) Four-week intravenous toxicity study in monkeys (4.2.3.7.5-2)

Following 4-week intravenous administration of 1, 3, or 10 mg/kg/day of M-II (2*S*, 8*S*) to monkeys (3 monkeys/sex/group), there were no treatment-related changes. Thus, the NOAEL was determined to be 10 mg/kg/day. The M-II (2*S*, 8*S*) exposure ($AUC_{0\text{-}24h}$[8)]) at the NOAEL was ≥30-fold the human exposure at the clinical dose of 8 mg.

(b) Embryo-fetal developmental toxicity study in rats (4.2.3.7.5-4)

Pregnant rats (n = 16-17/group) were intravenously administered M-II (2*S*, 8*S*) at doses of 10 or 30 mg/kg/day from gestation day 6 to 17. Since maternal, fetal, and placental examinations revealed no abnormalities, the maternal and embryo-fetal NOAELs were both determined to be 30 mg/kg/day.

3.(iii).A.(7).3) Toxicity studies on impurities

(a) Toxicity studies on U-5

A single oral dose of 2000 mg/kg of Ramelteon containing 0.12% of U-5 or less than the quantifiable level (0.02%) of U-5 was administered to rats (5 rats/sex/group) to compare acute toxicity. As a result, there were no differences in toxicological profile and acute toxicity was considered comparable (4.2.3.7.6-1).

Ramelteon containing 0.1% of U-5 was not mutagenic in a bacterial reverse mutation assay (4.2.3.7.6-3).

(b) Toxicity studies on U-6

Rats (10 rats/sex/group) were orally administered 150 mg/kg/day of Ramelteon containing 0.1% of U-6 or less than the quantifiable level (0.02%) of U-6 for 4 weeks to compare repeat-dose toxicity. As a result, there were no differences in toxicological profile and repeat-dose toxicity was considered comparable (4.2.3.7.6-2).

Ramelteon containing 0.1% of U-6 was not mutagenic or clastogenic in a bacterial reverse mutation assay and a chromosomal aberration assay in CHL cells (4.2.3.7.6-4, 4.2.3.7.6-5).

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

PMDA asked the applicant to explain the toxicological significance of vacuolization of the cortical cells of the adrenal gland and ovarian interstitial cells observed in rat repeat-dose toxicity studies.

The applicant explained as follows:

Adrenal cortical cells and ovarian interstitial cells store cholesteryl esters as lipid droplets for steroid synthesis, and a decrease in steroid synthesis/secretion results in increased storage of cholesteryl esters (Casarett LJ, Doull J, Klaassen CD eds, *Casarett & Doull's Toxicology*, McGraw-Hill Medical Pub, 2001;711-759). It has been reported that melatonin inhibits the secretion of ACTH, glucocorticoids, and gonadotropins (Preslock JP, *Endocr Rev*, 1984;5: 282-308). Thus, it is considered that vacuolization of adrenal cortical cells and ovarian interstitial cells reflects the inhibition of steroid hormone synthesis/secretion associated with the pharmacological effects of Ramelteon. In studies where the effects

on blood hormone levels were assessed following 5-week oral administration of 15 to 250 mg/kg/day of Ramelteon to female rats or 4-week oral administration of 15 to 1000 mg/kg/day of Ramelteon to male rats (Reference data 4.2.3.4.3-6, Reference data 4.2.3.4.3-7), estradiol concentrations were not affected and dehydroepiandrosterone (DHEA) and corticosterone levels were elevated. Vacuolization did not occur at a lower dose and was not exacerbated with prolonged duration of treatment. Therefore, even if steroid synthesis/secretion from adrenal cortical cells and ovarian interstitial cells are reduced, hormonal homeostasis will not be affected significantly.

PMDA asked the applicant to explain the mechanism of the development of neoplastic lesions (hepatic tumors, Harderian gland adenomas, Leydig cell tumors of the testis) observed in carcinogenicity studies and their relevance to humans.

The applicant explained about hepatic tumors as follows:
In a 13-week oral administration study conducted for dose selection for a mouse carcinogenicity study (4.2.3.4.1-2) and a 4-week repeat-dose study in rats (4.2.3.2-3), hepatic drug-metabolizing enzyme activity was increased at ≥100 and ≥150 mg/kg/day, respectively and these doses were almost correlated with the doses associated with an increased incidence of hepatic tumors. The drug-metabolizing enzymes induced by phenobarbital (PB) (a typical hepatic drug-metabolizing enzyme inducer and a liver tumor promotor) in a 1-week oral administration study (Reference data 4.2.3.4.3-2, Reference data 4.2.3.4.3-3) were compared with those induced by Ramelteon. As a result, the CYP isoforms induced were similar. Therefore, it is considered that the development of hepatic tumors associated with Ramelteon is attributed to tumor promotion due to the induction of hepatic drug-metabolizing enzymes. Based on epidemiological studies, PB has not been found to cause human tumors (Whysner J et al, *Pharmacol Ther*, 1996;71: 153-191) and mouse and rat hepatic tumors through this promoting mechanism are of little relevance to humans (Monro A, *Exp Toxicol Pathol*, 1996;48: 155-166, Willams GM et al, *Exp Toxic Pathol*, 1996;48: 189-195, Williams GM, *Cancer Lett*, 1997;117: 175-188). In a study in which 15 to 1000 mg/kg/day of Ramelteon was orally administered for 4 weeks to male rats and the effects on blood hormone concentrations and liver tissue were assessed (Reference data 4.2.3.4.3-7), Ramelteon at ≥250 mg/kg/day produced an increase in DHEA (a coricosteroid), which is known to be a peroxisome proliferator. It has been shown that long-term treatment with DHEA induced hepatocellular adenomas and hepatocellular carcinomas in the rat and DHEA has a tumor-promoting effect in rat liver (Mayer D et al, *Toxicol Pathol*, 2003;31: 103-112). Therefore, although the possibility that an increase in endogenous DHEA enhanced tumor promotion related to the induction of hepatic drug-metabolizing enzymes can not be ruled out, it has been reported that the induction of hepatic tumors by peroxisome proliferators is also specific to mice and rats (Williams GM, *Cancer Lett*, 1997;117: 175-188).

The applicant explained about Harderian gland adenomas observed in a mouse carcinogenicity study as follows:
It has been suggested that melatonin affects cell differentiation in the Harderian glands of hamsters directly or by changing thyroid hormone concentrations (Coto-Montes AM et al, *Endocrine Research*, 1993;19: 101-111) and it has been reported that long-term daily melatonin infusion induces the hypertrophy of the

Harderian gland in hamsters (Djeridane Y et al, *J Pineal Res*, 2000;29: 65-73). An *in vitro* study (Reference data 4.2.3.4.3-11) showed that Ramelteon and its metabolites inhibited melatonin metabolism in rat hepatic microsomes. In a 4-week oral administration study of Ramelteon at 3 to 300 mg/kg/day in aged mice (62-63 weeks of age) (Reference data 4.2.3.4.3-3), plasma thyroid hormone levels were not affected, but Ramelteon at ≥30 mg/kg/day produced increases in plasma and Harderian gland melatonin levels. A persistent increase in melatonin levels may be involved in an increased incidence of Harderian gland adenomas. Meanwhile, plasma melatonin levels were increased at ≥60 mg/kg/day in a rat 4-week oral administration study of Ramelteon at 15 to 1000 mg/kg/day (Reference data 4.2.3.4.3-7), but there were no effects on the Harderian gland in the rat carcinogenicity study. Therefore, the development of Harderian gland adenoma is considered specific to mice. As the Harderian gland is an organ unique to rodents and humans do not have an organ/tissue equivalent to the rodent Harderian gland, Harderian gland adenoma is considered of no relevance to humans.

The applicant explained about Leydig cell tumors of the testis as follows:
In studies where male rats were orally administered 6 to 200 mg/kg/day of Ramelteon for 1 week or 250 or 1000 mg/kg/day of Ramelteon for 4 weeks and the effects on plasma hormone concentrations were assessed (Reference data 4.2.3.4.3-5, Reference data 4.2.3.4.3-10), a reduction in plasma testosterone concentrations at Week 1 at 200 mg/kg/day and a reduction in plasma testosterone concentrations and an increase in luteinizing hormone (LH) concentrations at Week 4 at ≥250 mg/kg/day were observed and these doses were almost consistent with those associated with an increased incidence of Leydig cell tumors. Thus, the development of Leydig cell tumors is considered due to decreased testosterone and consequent elevated LH. It has been reported that the development of Leydig cell tumors of the testis in rats involving this negative feedback mechanism of the hypothalamic-pituitary-testis axis is of little relevance to humans (Prentice DE et al, *Human & Exp Toxicol*, 1995;14: 562-572, Cook JC et al, *Crit Rev Toxicol*, 1999;29: 169-261) and the human risk should be low.

PMDA asked the applicant to explain the cause of decreased blood testosterone, which has been proposed as the mechanism behind Leydig cell tumors of the testis observed in a rat carcinogenicity study, and the human safety.

The applicant explained as follows:
As melatonin has been reported to inhibit gonadotropin secretion from the pituitary gland (Preslock JP, *Endocr Rev*, 1984;5: 282-308), treatment with Ramelteon may have also resulted in decreased steroid synthesis/secretion from Leydig cells of the testis through a similar mechanism. However, in a study where 6 to 200 mg/kg/day of Ramelteon was orally administered for 1 week to rats and blood levels of various hormones were measured (Reference data 4.2.3.4.3-5), no alterations in the concentrations of any of gonadotropins including LH were noted at the dose associated with suppressed plasma testosterone levels (200 mg/kg/day). In a 4-week oral administration study of Ramelteon at 250 or 1000 mg/kg/day in male rats (Reference data 4.2.3.4.3-10), elevated LH levels with decreased plasma testosterone levels were observed. Thus, the inhibition of testosterone synthesis/secretion via the pituitary gland is unlikely. As it has been reported that melatonin receptors are present also in Leydig cells of the testis and melatonin

reduces cAMP and suppresses an increase in intracellular Ca concentration, resulting in the inhibition of steroid synthesis in Leydig cells (Valenti S et al, *Ann NY Acad Sci*, 2002;966: 284-289), there is a possibility that Ramelteon suppresses plasma testosterone levels via melatonin receptors present in Leydig cells of the testis. In some of Japanese and foreign clinical studies, blood hormone levels were measured (Japan, 5.3.5.2-1.1, OCT002; Overseas, 5.3.5.4-9, TL031; 5.3.5.4-10, TL032; 5.3.5.2-2, TL022). As a result, while a minimal decrease in testosterone was observed in Study TL022, an increase in testosterone was also noted in other studies and there was no consistent trend, indicating that there is no effect at the clinical dose.

PMDA asked the applicant to explain whether non-neoplastic lesions observed in mouse and rat carcinogenicity studies can occur in humans and discuss whether patients are at risk of retinal damage after exposure to the sun light etc. as retinal atrophy was observed in rats.

The applicant explained as follows:
When the exposures of unchanged Ramelteon and different metabolites at the NOAEL for the main non-neoplastic lesions possibly related to Ramelteon in the carcinogenicity studies (100 mg/kg/day for mice, 15 mg/kg/day for rats) are compared with the human exposures at the clinical dose of 8 mg ($AUC_{0\text{-}24h}$[8)]), the mouse-to-human safety margins are all ≥20-fold and the rat-to-human safety margins are all ≥10-fold. Thus, any of these non-neoplastic lesions will not become a problem in clinical use in humans.
Regarding retinal atrophy in rats, the albino rat retina is generally very sensitive to light and the albino rat is more susceptible to retinal atrophy than the pigmented rat (Imai R et al, *J Vet Med Sci*, 1993;55: 367-370). On the other hand, as it has also been reported that melatonin increases retinal light damage in the albino rat (Sugawara T et al, *Invest Ophthalmol Vis Sci*, 1998;39: 2458-2465), an increased incidence of retinal atrophy in rats may be associated with the pharmacological effects of Ramelteon. However, as this increased incidence was noted at 1000 mg/kg/day only, which was extremely higher than the therapeutic dose in monkeys (0.03-0.3 mg/kg) or the clinical dose in humans (8 mg), this finding is not considered associated with the pharmacological effects of Ramelteon, and taking into account that there was a significant reduction in body weight gain at this dose level, it seems that the incidence of naturally occurring lesions was increased due to the deteriorated conditions of animals. Furthermore, retinal atrophy was not noted in the carcinogenicity study in pigmented B6C3F1 mice or a 39-week administration study in monkeys and it appears that pigmented animals are less susceptible to retinal atrophy. When the exposures of unchanged Ramelteon and metabolites including the major metabolite (M-II) ($AUC_{0\text{-}24h}$) at the dose not associated with an increased incidence of retinal atrophy in the rat are compared with the human exposures at the clinical dose of 8 mg, the safety margins are ≥13-fold. The half-life of blood Ramelteon was about 1 to 2 hours for both unchanged Ramelteon and the major metabolite and there was no evidence of accumulation. As Ramelteon is taken at bedtime, patients are unlikely to be exposed to the sun light when blood concentrations are high. Taking account of these points, the risk of retinal damage in humans is very low.

PMDA accepted the above and concluded that there is no particular toxicological problem.

4. Clinical data

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

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

As the evaluation data, the results from a Japanese food effect study (5.3.1.1-2, CPH007) etc. were submitted. As the reference data, the results from a foreign bioavailability (BA) study (5.3.1.1-1, EC003) etc. were submitted. Serum concentrations of unchanged Ramelteon and metabolites were determined using a validated LC/MS/MS method (Lower limit of quantitation, 0.05 ng/mL for unchanged Ramelteon, 0.5 ng/mL for metabolites). ^{14}C-Ramelteon-derived radioactivity was determined by liquid scintillation counter (Lower limit of quantitation, [redacted] times the background radioactivity).

The proposed commercial formulation (the 8 mg tablet) was used in a Japanese phase III study (5.3.5.1-3.1, CCT003) and the 4 mg tablet formulation was also used in a Japanese phase II/III study (5.3.5.1-2.1, CCT002) and the two formulations showed comparable dissolution profiles. Although the tablets of different formulations and strengths (the phase I and phase II/III formulations) were used in Japanese phase I studies and foreign clinical studies, these tablet formulations were determined to be comparable to the proposed commercial formulation due to the similarity of the dissolution behaviors etc.

4.(i).A.(1) Food effect (5.3.1.1-2, CPH007)

A crossover study was conducted to assess the effect of food on the pharmacokinetics of Ramelteon in Japanese healthy adult male subjects (18 subjects included in pharmacokinetic assessment). Subjects received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning in the fasted state or after breakfast. The mean ratio of fed to fasted state with its 90% CI was 0.96 [0.71, 1.30] for C_{max} and 1.30 [1.01, 1.67] for $AUC_{0\text{-}inf}$ and the 90% CI did not fall within the range of 0.8 to 1.25 for either C_{max} or $AUC_{0\text{-}inf}$.

4.(i).A.(2) Absolute bioavailability (BA) (Reference data 5.3.1.1-1, EC003)

A crossover study in foreign healthy adult male subjects (18 subjects included in pharmacokinetic analysis) was conducted to determine the oral bioavailability. A single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) or a single intravenous dose of 2 mg of Ramelteon was administered. The oral bioavailability calculated from the $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon was 1.77%. The major metabolite in serum was M-II for both the intravenous and oral doses. After the intravenous dose, the serum $AUC_{0\text{-}inf}$ was similar for unchanged Ramelteon and M-II. However, after the oral dose, the serum $AUC_{0\text{-}inf}$ was approximately 60-fold higher for M-II than for unchanged Ramelteon. These data suggest that orally administered Ramelteon undergoes extensive first-pass metabolism.

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

4.(i).B.(1) Food effect

Since it was suggested that the pharmacokinetics of Ramelteon are affected by food, PMDA asked the applicant to explain whether the timing of taking Ramelteon may affect its efficacy and safety, and whether the timing of dosing should be specified.

The applicant explained as follows:
In a food effect study using the proposed commercial formulation (5.3.1.1-2, CPH007), the 90% CI for the fed to fasted C_{max} ratio for unchanged Ramelteon fell slightly outside the bioequivalence criteria (0.8-1.25) and the $AUC_{0\text{-}inf}$ was approximately 30% higher after fed administration. As it has been suggested that not only unchanged Ramelteon but also its major metabolite M-II binds to the MT_1 receptor and is active (4.2.1.1-2, 4.2.1.1-3), the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of M-II (fed administration/fasted administration) with their 90% CIs were determined, which were 72.3 [63.1, 82.9] and 93.8 [89.3, 98.5], respectively, and the $AUC_{0\text{-}inf}$ was unaffected, but the C_{max} was affected by food. Based on the results from a pharmacokinetic study in Japanese healthy adult subjects (5.3.3.1-1, CPH001), the exposure at the clinical dose of 8 mg in fed subjects would not exceed the exposure at 16 mg in fasted subjects. In Japanese and foreign food effect studies (5.3.3.1-1, CPH001; 5.3.1.1-2, CPH007; Reference data 5.3.1.1-3, TL004), there were no major differences in the nature or incidence of adverse events between fasted and fed subjects. Furthermore, the safety of 16 mg of Ramelteon has been assured. Taking account of these findings, an increase in Ramelteon exposure after fed administration of 8 mg of Ramelteon is unlikely to become a major safety problem. However, the T_{max} was delayed under fed conditions compared to fasted conditions (unchanged Ramelteon, 0.75 hours under fasted conditions, 0.88 hours under fed conditions; M-II, 0.75 hours under fasted conditions, 1.75 hours under fed conditions) and the onset of action of Ramelteon may be delayed. Therefore, it will be advised in the package insert that Ramelteon should not be taken with food or immediately after a meal.

Although the pharmacokinetics of Ramelteon were affected by food, there were no major differences in the safety according to the timing of dosing and no clinically relevant events were reported. Therefore, PMDA accepts the above, but considers that it is necessary to continue to investigate the food effect under routine uses of Ramelteon also via post-marketing surveillance.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the results from Japanese phase I studies in healthy adult male subjects (5.3.3.1-1, CPH001; 5.3.3.1-2, CPH002; 5.3.3.1-3, CPH006) and a Japanese study in elderly subjects (5.3.3.3-1, CPH005) were submitted. As the reference data, the results from foreign phase I studies in healthy adult subjects (Reference data 5.3.3.1-4, EC004; Reference data 5.3.3.1-5, PNFP001; Reference data 5.3.3.1-6, EC002), foreign studies in special populations (Reference data 5.3.3.3-2, TL003; Reference data 5.3.3.3-3, TL029; Reference data 5.3.3.3-4, TL030), and foreign drug interaction studies (Reference data 5.3.3.4-1, TL007; Reference data 5.3.3.4-2, TL009; Reference data 5.3.3.4-3, TL049; Reference data 5.3.3.4-4, TL034; Reference data 5.3.3.4-5, TL036; Reference data 5.3.3.4-6, TL035; Reference data 5.3.3.4-7, TL026; Reference data 5.3.3.4-8, TL027; Reference data 5.3.3.4-9, TL024; Reference data 5.3.3.4-10, TL033; Reference data 5.3.3.4-11, TL037; Reference data 5.3.3.4-12, TL028; Reference data 5.3.3.4-13, TL043; Reference data 5.3.3.4-14, TL050; Reference data 5.3.3.4-15, TL054; Reference data 5.3.3.4-16, TL056; Reference data 5.3.3.4-17, TL070) were submitted. The results from *in vitro* studies using human biomaterials (4.2.2.3-9, 4.2.2.3-10, 4.2.2.3-11, 4.2.2.4-1, 4.2.2.4-8, 4.2.2.4-10, 4.2.2.4-11, 4.2.2.4-12, 4.2.2.4-13, 4.2.2.4-14, 4.2.2.6-1, 4.2.2.6-2, 4.2.2.6-3, 4.2.2.6-4, 4.2.2.6-5) etc. were also submitted. Unless

otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(ii).A.(1) Studies using human biomaterials

When ^{14}C-Ramelteon was added *in vitro* to human blood at final concentrations of 0.01 to 1 μg/mL, the distribution in blood cells was 20.9% to 22.0% (4.2.2.3-9).

When ^{14}C-Ramelteon was added to human plasma, human serum albumin (HSA), α_1-acid glycoprotein (AGP), and a mixture of HSA and AGP at final concentrations of 0.01 to 1 μg/mL, the *in vitro* ([redacted]) protein binding was 85.1% to 88.1%, 72.7% to 76.2%, 56.3% to 62.9%, and 83.3% to 84.6%, respectively. The human serum protein binding of M-II (2*S*, 8*S*) was 76.5% to 79.1% (4.2.2.3-10, 4.2.2.3-11).

When 50 μM of ^{14}C-Ramelteon was added to human hepatic microsomes, the primary metabolites were M-II, M-V, and M-VII. In addition, M-III, M-VIII ([redacted]), and M-IX were also detected (4.2.2.4-1).

Following a single oral dose of 2 mg of Ramelteon in Japanese healthy adult male subjects, M-II detected in serum was M-II (2*S*, 8*S*) only (4.2.2.4-8).

Following a single oral dose of 8 mg of Ramelteon in foreign healthy adult subjects, the (*S*) form only was detected in serum at 1 and 2 hours post-dose (4.2.2.4-10).

Using microsomes expressing 10 different human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C19, CYP2D6, CYP2E1, CYP3A4), the CYP isoforms involved in the metabolism of ^{14}C-Ramelteon were investigated. As a result, the involvement of CYP1A1, CYP1A2, CYP2C19, and CYP3A4 in the metabolism of Ramelteon was suggested. In human hepatic microsomes, the highest metabolic correlation was between ^{14}C-Ramelteon and CYP1A2, indicating that Ramelteon is metabolized principally by CYP1A2 (4.2.2.4-11).

Using microsomes expressing 10 different human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C19, CYP2D6, CYP2E1, CYP3A4), the CYP isoforms involved in the metabolism of M-II (2*S*, 8*S*) were investigated. As a result, the involvement of CYP2C19 and CYP3A4 in the metabolism of M-II (2*S*, 8*S*) was suggested. In human hepatic microsomes, the highest metabolic correlation was between M-II (2*S*, 8*S*) and CYP3A4, indicating that M-II is metabolized principally by CYP3A4 (4.2.2.4-12).

Using microsomes expressing 11 different human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C9*2, CYP2C19, CYP2D6, CYP2E1, CYP3A4) and their specific substrates, the inhibition of CYP isoforms by Ramelteon or M-II (2*S*, 8*S*) was assessed. The IC_{50} values of Ramelteon for CYP2C8, CYP2C19, and CYP3A4 were 10 to 100 μM and its IC_{50} values for other CYP isoforms were ≥100 μM and the IC_{50} values of M-II (2*S*, 8*S*) for CYP isoforms were ≥100 μM (4.2.2.4-13).

Human primary hepatocytes were added with Ramelteon (3-30 μM), M-II (3-30 μM), or rifampicin (10 μM) and CYP3A activity as measured by testosterone 6β-hydroxylation was determined. Ramelteon weakly induced CYP3A activity compared with the positive control rifampicin while M-II did not apparently induce CYP3A activity even at the highest concentration (4.2.2.4-14).

An *in vitro* metabolism study of Ramelteon using human hepatic microsomes was conducted to assess drug-drug interactions. Fluvoxamine (a CYP1A2 inhibitor) and fluconazole (a CYP2C9 inhibitor) inhibited the metabolism of Ramelteon by 60.8% to 64.7% and 46.7% to 48.0%, respectively (4.2.2.6-1).

An *in vitro* metabolism study of ^{14}C-Ramelteon using human hepatic microsomes was conducted to assess drug-drug interactions. The IC_{50} values of fluvoxamine for the inhibition of clearance of unchanged Ramelteon and M-II formation were 1.7 and 0.20 μM, respectively, and the IC_{50} values of ketoconazole were 1.8 and 21 μM, respectively (4.2.2.6-2).

The effect of fluvoxamine on the metabolism of ^{14}C-Ramelteon was studied using human hepatic microsomes. The Ki values of fluvoxamine for the inhibition of clearance of unchanged Ramelteon and M-II formation were 0.49 and 0.14 μM, respectively, showing that fluvoxamine has a potent inhibitory effect (4.2.2.6-3).

The effect of fluvoxamine on the metabolism of Ramelteon was studied using human hepatic microsomes. The Ki value of fluvoxamine for the inhibition of clearance of unchanged Ramelteon was 0.16 μM, which was similar to that for ^{14}C-Ramelteon (4.2.2.6-4).

In human hepatic microsomes, the highest metabolic correlation was between Ramelteon and CYP1A2 activity in the absence of fluvoxamine while there was no correlation with CYP1A2 activity in the presence of fluvoxamine, suggesting that fluvoxamine inhibits Ramelteon metabolism by CYP1A2 (4.2.2.6-5).

4.(ii).A.(2) Studies in healthy adult subjects

Japanese data

Japanese healthy adult male subjects (8 subjects for each step) received a single oral dose of 0.3, 1, 2, 4, 8, or 16 mg of Ramelteon (the phase I 0.1 mg, 1 mg, and 4 mg tablet formulations) in the morning in the fasted state. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II were as shown in the following table. Although the C_{max} and $AUC_{0\text{-}24h}$ of serum unchanged Ramelteon at 4 mg were lower than those at 2 mg, its cause was unclear. The C_{max} and $AUC_{0\text{-}24h}$ of serum M-II increased dose-dependently (5.3.3.1-1, CPH001).

Table. Pharmacokinetic parameters following single oral doses of Ramelteon in Japanese healthy adult male subjects

		0.3 mg	1 mg	2 mg	4 mg	8 mg	16 mg
Unchanged Ramelteon	C_{max} (ng/mL)	0.06 ± 0.09	0.09 ± 0.10	0.48 ± 0.41	0.30 ± 0.22	1.82 ± 1.54	4.19 ± 4.61
	t_{max} (h)	0.58 ± 0.14[a)]	0.60 ± 0.14[b)]	0.69 ± 0.18	0.72 ± 0.25	0.66 ± 0.27	0.63 ± 0.23
	$t_{1/2}$ (h)	-	0.75[c)]	0.64 ± 0.16[a)]	0.67 ± 0.43[d)]	0.87 ± 0.34[e)]	0.89 ± 0.13[e)]
	$AUC_{0\text{-}24h}$ (ng·h/mL)	0.03 ± 0.05	0.08 ± 0.11	0.64 ± 0.61	0.33 ± 0.21	1.89 ± 1.31	6.08 ± 7.00
M-II	C_{max} (ng/mL)	2.53 ± 0.46	8.58 ± 1.90	15.99 ± 4.00	31.35 ± 8.66	63.89 ± 19.54	138.57 ± 43.00
	t_{max} (h)	0.75 ± 0.19	0.69 ± 0.12	0.84 ± 0.13	0.91 ± 0.42	0.81 ± 0.26	0.78 ± 0.36
	$t_{1/2}$ (h)	1.43 ± 0.27[f)]	1.70 ± 0.16[e)]	1.77 ± 0.36[d)]	1.63 ± 0.09[b)]	1.88 ± 0.17[d)]	2.07 ± 0.27[f)]

	$AUC_{0\text{-}24h}$ (ng·h/mL)	5.62 ± 2.50	19.47 ± 5.42	48.25 ± 18.35	82.31 ± 19.61	195.64 ± 50.00	445.14 ± 116.42

a) n = 3, b) n = 5, c) n = 1, d) n = 6, e) n = 4, f) n = 7

Japanese healthy adult male subjects (8 subjects per dose group) were orally administered 8 or 16 mg of Ramelteon (the phase I 4 mg tablet formulation) once daily 3 hours after the evening meal (2 hours prior to bedtime) for 7 days. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II on Days 1 and 7 were as shown in the following table. The C_{max} and $AUC_{0\text{-}24h}$ of serum unchanged Ramelteon at 16 mg on Day 7 were higher than those on Day 1, which was considered due to the large variability caused by the low bioavailability of Ramelteon. Trough levels were below the lower limit of quantitation at both doses and there were no major differences in the pharmacokinetic parameters of the major metabolite M-II between Days 1 and 7. Therefore, there was no evidence of accumulation (5.3.3.1-2, CPH002).

Table. Pharmacokinetic parameters following multiple oral doses of Ramelteon in Japanese healthy adult male subjects

			C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Unchanged Ramelteon	8 mg	Day 1	1.39 ± 1.05	1.31 ± 0.84	1.08 ± 0.23[a)]	2.34 ± 1.01
		Day 7	1.47 ± 1.03	1.09 ± 0.38	0.92 ± 0.31[b)]	2.64 ± 1.40
	16 mg	Day 1	1.85 ± 2.91	1.22 ± 0.47	1.25 ± 0.25[c)]	4.23 ± 6.45
		Day 7	2.42 ± 3.63	1.31 ± 0.46	1.32 ± 0.61[c)]	6.08 ± 9.46
M-II	8 mg	Day 1	54.18 ± 21.20	1.53 ± 0.80	2.26 ± 0.42[b)]	234.79 ± 62.20
		Day 7	54.15 ± 10.53	1.53 ± 0.54	2.05 ± 0.54[b)]	229.07 ± 66.03
	16 mg	Day 1	75.58 ± 24.39	1.72 ± 0.65	2.12 ± 0.36	339.48 ± 124.17
		Day 7	76.60 ± 23.17	2.00 ± 0.85	2.17 ± 0.41	380.39 ± 148.19

a) n = 5, b) n = 6, c) n = 7

Japanese healthy adult male subjects (8 subjects receiving a single dose, 8 subjects receiving multiple doses) were orally administered 32 mg of Ramelteon (the phase I 1 mg and 10 mg tablet formulations) as a single dose in the morning in the fasted state or once daily 3 hours after the evening meal for 7 days. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II were as shown in the following table. Although the C_{max} and $AUC_{0\text{-}24h}$ of serum unchanged Ramelteon on Day 7 were higher than those on Day 1, no major alternations in serum M-II concentrations were seen following multiple-dose administration (5.3.3.1-3, CPH006).

Table. Pharmacokinetic parameters following a single oral dose or multiple oral doses of Ramelteon in Japanese healthy adult male subjects

			C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Unchanged Ramelteon	Single dose		4.02 ± 4.28	0.75 ± 0.23	1.01 ± 0.13[a)]	5.63 ± 5.09
	Multiple doses	Day 1	2.58 ± 1.47	1.06 ± 0.40	1.23 ± 0.23[b)]	5.90 ± 3.77
		Day 7	3.30 ± 3.13	1.28 ± 0.49	1.18 ± 0.16[b)]	7.01 ± 5.78
M-II	Single dose		249.93 ± 105.95	0.84 ± 0.23	1.63 ± 0.15[c)]	686.43 ± 201.17
	Multiple doses	Day 1	180.04 ± 40.95	1.56 ± 0.32	2.35 ± 0.45	841.10 ± 246.96
		Day 7	189.68 ± 51.01	1.59 ± 0.50	2.17 ± 0.23	824.09 ± 226.37

a) n = 4, b) n = 6, c) n = 5

Foreign data

Six foreign healthy adult male subjects received a single oral dose of 16 mg of ^{14}C-Ramelteon in the morning in the fasted state. Serum radioactivity reached its C_{max} of 552 ± 1.26 ng eq./mL at 0.5 hours post-dose and was eliminated with a $t_{1/2}$ of 112 hours. Unchanged Ramelteon and metabolites M-I, M-II, M-III, M-IV, M-IX glucuronide, M-VIII glucuronide, etc. were detected in serum. Approximately 84.31% and 3.96% of the administered radioactivity were excreted in the urine and feces, respectively, up to 192 hours post-dose. The primary metabolites in the urine were M-VIII and its glucuronate conjugate (Reference data 5.3.3.1-4, EC004).

Foreign healthy adult male subjects (8 subjects per group) received a single oral dose of 4, 8, 16, 32, or 64 mg of Ramelteon (the phase I 1 mg, 4 mg, and 10 mg tablet formulations) in the morning in the fasted state. Serum unchanged Ramelteon reached its C_{max} (1.15 ± 1.25, 5.73 ± 5.58, 6.92 ± 5.32, 17.41 ± 13.21, and 25.86 ± 19.87 ng/mL, respectively) at 0.75 to 1 hours post-dose, and was eliminated with a $t_{1/2}$ of 0.8 to 1.9 hours. The $AUC_{0\text{-}inf}$ was 1.71 ± 1.95, 6.95 ± 7.50, 9.88 ± 7.68, 22.50 ± 18.10, and 36.10 ± 25.72 ng·h/mL, respectively. Serum M-II reached its C_{max} (34.40 ± 11.54, 73.01 ± 16.69, 129.34 ± 34.64, 283.63 ± 80.66, and 463.25 ± 112.90 ng/mL, respectively) at 0.75 to 1.25 hours post-dose, the $t_{1/2}$ was 2.3 to 3.4 hours, and the $AUC_{0\text{-}inf}$ was 101.92 ± 42.24, 224.62 ± 54.55, 384.86 ± 123.28, 914.87 ± 215.84, and 1515.45 ± 584.47 ng·h/mL, respectively. Both serum unchanged Ramelteon and M-II concentrations increased dose-dependently (Reference data 5.3.3.1-5, PNFP001).

Foreign healthy adult male subjects (10 subjects per group) were orally administered 16 or 64 mg of Ramelteon (the phase I 4 mg and 10 mg tablet formulations) once daily 3 hours after the evening meal for 7 days. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II were as shown in the following table. While the C_{max} and $AUC_{0\text{-}24h}$ of serum unchanged Ramelteon on Day 7 were higher than those on Day 1, the pharmacokinetic parameters of serum M-II were not significantly affected by multiple-dose administration (Reference data 5.3.3.1-6, EC002).

Table. Pharmacokinetic parameters following multiple oral doses of Ramelteon in foreign healthy adult male subjects

			C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	AUC[b)] (ng·h/mL)
Unchanged Ramelteon	16 mg	Day 1	1.58 ± 2.34	0.88 (0.50, 2.00)	1.49 ± 0.51	3.76 ± 7.00
		Day 7	2.58 ± 4.23	0.88 (0.50, 3.00)	1.27 ± 0.39	6.63 ± 14.08
	64 mg	Day 1	14.69 ± 25.78	0.75 (0.50, 2.00)	1.40 ± 0.63	23.71 ± 45.57
		Day 7	13.00 ± 13.49	0.75 (0.50, 2.00)	1.52 ± 0.57	25.16 ± 40.72
M-II	16 mg	Day 1	78.22 ± 30.54	1.50 (0.75, 3.00)	2.38 ± 0.66	325.67 ± 193.06
		Day 7	83.13 ± 26.84	1.50 (0.50, 3.00)	2.36 ± 0.63	343.69 ± 217.41
	64 mg	Day 1	388.0 ± 161.2	1.00 (0.50, 3.00)	2.72 ± 0.88	1380.33 ± 749.94
		Day 7	350.2 ± 93.9	1.00 (0.50, 3.00)	2.57 ± 0.73	1322.08 ± 744.79

a) Median (Min, Max)
b) $AUC_{0\text{-}inf}$ for Day 1, $AUC_{0\text{-}24h}$ for Day 7

4.(ii).A.(3) Intrinsic factors

Japanese data

1) Effect of age

Japanese healthy male subjects (12 elderly and 12 non-elderly subjects) received a single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the fasted state. The C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon were 31% and 85% higher, respectively, and the $t_{1/2}$ was 0.6 hours longer in

elderly subjects compared with non-elderly subjects. The C_{max} of serum M-II was similar, but the $AUC_{0\text{-}inf}$ was 28% higher in the elderly than in the non-elderly (5.3.3.3-1, CPH005).

Table. Pharmacokinetic parameters following a single oral dose of 16 mg of Ramelteon in Japanese healthy male subjects (elderly and non-elderly subjects)

		C_{max} (ng/mL)	t_{max} [a)] (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)
Unchanged Ramelteon	Non-elderly men	7.46 ± 6.95	0.75 (0.50, 2.00)	0.96 ± 0.19	10.29 ± 10.41
	Elderly men	10.81 ± 10.50	0.75 (0.50, 2.00)	1.59 ± 0.32	18.48 ± 15.71
M-II	Non-elderly men	128.16 ± 27.39	1.00 (0.75, 2.00)	2.30 ± 0.53	400.73 ± 120.01
	Elderly men	126.86 ± 32.30	1.50 (1.00, 2.00)	3.29 ± 0.75	514.59 ± 160.79

a) Median (Min, Max)

Foreign data

1) Effects of age and gender

Foreign healthy younger adult subjects (12 male and 12 female subjects) and foreign healthy elderly subjects (12 male and 12 female subjects) received a single oral dose of 16 mg of Ramelteon (the phase I 8 mg tablet formulation) in the fasted state. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II were as shown in the following table. The C_{max} and $AUC_{0\text{-}inf}$ values of serum unchanged Ramelteon and M-II were higher and the $t_{1/2}$ was longer in the elderly compared to the non-elderly. While there were no gender differences in the pharmacokinetic parameters of serum unchanged Ramelteon or M-II among elderly subjects, the C_{max} and $AUC_{0\text{-}inf}$ values of serum unchanged Ramelteon and M-II were higher in non-elderly women than in non-elderly men (Reference data 5.3.3.3-2, TL003).

Table. Pharmacokinetic parameters following a single oral dose of 8 mg of Ramelteon in foreign healthy younger adult and elderly subjects

		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)
Unchanged Ramelteon	Non-elderly men	5.86 ± 5.80	1.50 (0.75, 2.50)	1.48 ± 0.91	7.83 ± 6.01
	Non-elderly women	7.95 ± 9.24	1.50 (0.25, 2.50)	1.67 ± 0.62	13.09 ± 17.08
	Elderly men	12.00 ± 18.59	1.25 (0.75, 3.00)	2.27 ± 0.76	17.17 ± 23.69
	Elderly women	11.19 ± 7.35	1.00 (0.50, 3.00)	2.94 ± 1.38	20.18 ± 14.75
M-II	Non-elderly men	102.97 ± 33.40	2.00 (1.00, 3.00)	2.29 ± 0.27	333.35 ± 98.21
	Non-elderly women	117.53 ± 24.81	2.00 (0.75, 3.03)	2.56 ± 0.75	418.37 ± 152.75
	Elderly men	125.06 ± 34.24	1.50 (0.75, 3.00)	3.32 ± 0.54	476.28 ± 147.34
	Elderly women	124.77 ± 31.05	1.50 (0.75, 4.00)	3.11 ± 0.80	488.99 ± 145.85

2) Effect of hepatic function

Foreign subjects with mild or moderate hepatic impairment (Child-Pugh score of 5-6 or 7-9) and foreign healthy adult subjects[13)] (12 subjects per group) were orally administered 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning in the fasted state as a single dose or once daily for 5 days. The pharmacokinetic parameters of serum unchanged Ramelteon and M-II on Day 8 (the 5th day of multiple-dose administration) were as shown in the following table. In subjects with mild or moderate hepatic impairment compared to their healthy matched controls, the $AUC_{0\text{-}\tau}$ of serum unchanged Ramelteon after multiple doses was 3.6-fold and 10.7-fold higher, respectively, and the C_{max} was 2.5-fold and 8.4-fold higher, respectively, and the $t_{1/2}$ was also prolonged. The $t_{1/2}$ of serum M-II was prolonged in subjects with

13) Healthy adult subjects matched with each of the two groups of subjects with hepatic impairment by race, gender, age, body weight, and smoking status.

hepatic impairment while there were no major differences in the $AUC_{0-\tau}$ of serum M-II between subjects with hepatic impairment and their healthy matched controls (Reference data 5.3.3.3-3, TL029).

Table. Pharmacokinetic parameters following once daily oral administration of 16 mg of Ramelteon for 5 days in foreign healthy adult subjects and subjects with hepatic impairment

		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (ng·h/mL)
Unchanged Ramelteon	Subjects with mild hepatic impairment	24.6 ± 19.4	0.75 (0.50, 1.50)	1.77 ± 0.64	46.7 ± 41.5
	Their healthy matched controls	9.6 ± 10.3	0.63 (0.50, 1.00)	1.18 ± 0.30	10.3 ± 11.7
	Subjects with moderate hepatic impairment	105 ± 105	0.63 (0.25, 1.00)	3.85 ± 2.84	333 ± 446
	Their healthy matched controls	11.8 ± 12.0	1.00 (0.50, 1.50)	1.28 ± 0.33	20.3 ± 25.9
M-II	Subjects with mild hepatic impairment	124 ± 42.7	1.00 (0.50, 3.00)	3.28 ± 0.81	548 ± 185
	Their healthy matched controls	128 ± 31.0	0.88 (0.50, 1.00)	2.79 ± 0.86	426 ± 146
	Subjects with moderate hepatic impairment	86.9 ± 33.1	1.00 (0.50, 4.00)	6.39 ± 5.51	514 ± 136
	Their healthy matched controls	111 ± 34.5	1.50 (0.75, 2.00)	2.99 ± 0.84	524 ± 235

3) Effect of renal function

Twenty-nine foreign subjects with renal impairment (subjects with CLcr [mL/min/1.73 m^2] 50-80 (mild), 30-49 (moderate), or <30 (severe) and subjects who required hemodialysis) and 21 foreign healthy adult subjects[14)] were administered 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning in the fasted state as a single dose or once daily for 5 days. When the C_{max} and $AUC_{0-\tau}$ of serum unchanged Ramelteon on Day 8 (the 5th day of multiple-dose administration) in the four groups of subjects with impaired renal function were compared with those in their healthy matched controls, the C_{max} was 0.6-, 1.6-, 1.2-, and 0.7-fold, respectively, and the $AUC_{0-\tau}$ was 0.7-, 1.3-, 1.8-, and 0.5-fold, respectively. There was no major effect on the $t_{1/2}$. The C_{max} of serum M-II was 1.2-, 1.0-, 1.0-, and 0.9-fold, respectively, and the $AUC_{0-\tau}$of serum M-II was 1.3-, 0.8-, 1.4-, and 0.7-fold, respectively (Reference data 5.3.3.3-4, TL030).

14) Healthy adult subjects matched with each of the four groups of subjects with renal impairment by race, gender, age, body weight, and smoking status.

Table. Pharmacokinetic parameters following once daily oral administration of 16 mg of Ramelteon for 5 days in foreign healthy adult subjects and subjects with renal impairment

		n	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (ng·h/mL)
Unchanged Ramelteon	Subjects with mild renal impairment	8	9.6 ± 7.6	0.50 (0.50, 1.50)	1.73 ± 0.58	12.6 ± 11.8
	Their healthy matched controls	5	13.6 ± 10.4	0.75 (0.50, 1.00)	1.51 ± 0.29	15.9 ± 15.3
	Subjects with moderate renal impairment	5	13.7 ± 17.8	0.50 (0.50, 2.00)	1.36 ± 0.47	16.9 ± 23.1
	Their healthy matched controls	5	5.7 ± 3.4	0.75 (0.50, 2.00)	1.33 ± 0.51	8.4 ± 5.4
	Subjects with severe renal impairment	7	8.8 ± 7.2	0.75 (0.50, 1.50)	1.87 ± 0.34	14.5 ± 11.8
	Their healthy matched controls	7	8.1 ± 8.1	0.50 (0.50, 1.00)	1.27 ± 0.47	13.0 ± 15.9
	Hemodialysis subjects	8	7.9 ± 10.1	0.50 (0.25, 0.75)	1.20 ± 0.50[a)]	6.0 ± 6.3
	Their healthy matched controls	4	8.0 ± 5.3	0.63 (0.50, 0.75)	1.22 ± 0.23	9.2 ± 5.5
M-II	Subjects with mild renal impairment	8	168 ± 77.0	0.75 (0.50, 2.00)	2.61 ± 0.73	498 ± 154.7
	Their healthy matched controls	5	130 ±37.5	0.75 (0.75, 1.00)	2.44 ± 0.54	369 ± 108.2
	Subjects with moderate renal impairment	5	91.2 ± 30.2	0.75 (0.50, 2.00)	2.50 ± 1.06	274 ± 120.9
	Their healthy matched controls	5	89.3 ± 25.2	1.00 (0.75, 2.00)	2.88 ± 0.97	332 ± 108.2
	Subjects with severe renal impairment	7	117 ± 35.3	1.00 (0.50, 3.00)	3.42 ± 1.05	514 ± 185.1
	Their healthy matched controls	7	115 ± 46.8	1.00 (0.50, 4.00)	2.29 ± 1.06[b)]	388 ± 206.7
	Hemodialysis subjects	8	125 ± 61.8	0.63 (0.50, 1.00)	3.90 ± 1.73[a)]	273 ± 90.2
	Their healthy matched controls	4	128 ± 20.5	0.88 (0.50, 1.00)	2.58 ± 0.59	378 ± 87.1

a) n = 7, b) n = 6

4.(ii).A.(4) Drug-drug interactions

4.(ii).A.(4).1) Ketoconazole

Foreign healthy adult subjects (26 subjects included in pharmacokinetic assessment) received a single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning or 200 mg of oral ketoconazole twice daily for 4 days (a morning dose only on Day 4) plus a single oral dose of 16 mg of Ramelteon in the morning on Day 4. The mean ratios of C_{max} and AUC_{0-inf} of serum unchanged Ramelteon (Ramelteon + ketoconazole/Ramelteon alone) with their 90% CIs were 1.36 [1.10, 1.68] and 1.84 [1.57, 2.16], respectively, and the mean ratios of C_{max} and AUC_{0-inf} of serum M-II with their 90% CIs were 1.23 [1.13, 1.34] and 1.93 [1.82, 2.05], respectively. Coadministration with ketoconazole increased the exposures to unchanged Ramelteon and M-II (Reference data 5.3.3.4-1, TL007).

4.(ii).A.(4).2) Fluconazole

Foreign healthy adult subjects (24 subjects included in pharmacokinetic assessment) received a single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning or multiple oral doses of fluconazole in the morning (200 mg twice daily on Day 1 and once daily on Days 2 through 4) plus 16 mg of Ramelteon on Day 4. The mean ratios of C_{max} and AUC_{0-inf} of serum unchanged Ramelteon (Ramelteon + fluconazole/Ramelteon alone) with their 90% CIs were 2.44 [1.93, 3.08] and 2.52 [2.15, 2.95], respectively, and the mean ratios of C_{max} and AUC_{0-inf} of serum M-II with their 90% CIs were 1.55 [1.43, 1.68] and 2.99 [2.75, 3.25], respectively. Coadministration with fluconazole increased the exposures to unchanged Ramelteon and M-II (Reference data 5.3.3.4-2, TL009).

4.(ii).A.(4).3) Fluvoxamine (FLV)

Foreign healthy adult subjects (47 subjects included in pharmacokinetic assessment) received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning on Day 1 followed by 3 days of washout and then received 200 mg of oral FLV once daily in the morning on Days 5 through 11

plus 8 mg of Ramelteon on Day 11 (Treatment sequence I) or received a single oral dose of 200 mg of FLV in the morning on Day 1 followed by 3 days of washout and then received 8 mg of Ramelteon once daily in the morning on Days 5 through 11 plus 200 mg of FLV on Day 11 (Treatment sequence II). The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + FLV/Ramelteon alone) with their 90% CIs were 28.1 [19.8, 39.8] and 82.6 [59.7, 114.3], respectively, and coadministration with FLV increased the exposure to unchanged Ramelteon markedly and increased the $t_{1/2}$ by 1.8 hours. Coadministration with FLV slightly increased the $AUC_{0\text{-}inf}$ of serum M-II with the mean ratio of 1.30 [1.09, 1.56], but decreased the C_{max} of serum M-II to about one-third with the mean ratio of 0.34 [0.27, 43.0] and prolonged the $t_{1/2}$ of serum M-II (8.2 hours vs. 2.6 hours). The pharmacokinetic parameters of plasma FLV were unaffected by coadministration with Ramelteon (Reference data 5.3.3.4-3, TL049).

4.(ii).A.(4).4) Fluoxetine

Foreign healthy adult subjects (27 subjects included in pharmacokinetic assessment) received a single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning or 40 mg of oral fluoxetine once daily in the morning for 11 days plus 16 mg of Ramelteon on Day 11. The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + fluoxetine/Ramelteon alone) with their 90% CIs were 1.40 [1.18, 1.66] and 1.50 [1.27. 1.77], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 1.17 [1.08, 1.26] and 1.52 [1.43, 1.61], respectively. Coadministration with fluoxetine increased the exposures to unchanged Ramelteon and M-II (Reference data 5.3.3.4-4, TL034).

4.(ii).A.(4).5) Omeprazole

Foreign healthy adult subjects (29 subjects included in pharmacokinetic assessment) were orally administered 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) alone, 40 mg of omeprazole alone, or Ramelteon 16 mg plus omeprazole 40 mg once daily in the morning in the fasted state for 7 days. The mean ratios of C_{max} and $AUC_{0\text{-}\tau}$ of serum unchanged Ramelteon (Ramelteon + omeprazole/Ramelteon alone) with their 90% CIs were 0.73 [0.59, 0.90] and 0.67 [0.60, 0.76], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}\tau}$ of serum M-II with their 90% CIs were 1.16 [1.07, 1.26] and 1.29 [1.23, 1.36], respectively. Coadministration with omeprazole decreased serum unchanged Ramelteon concentrations and increased serum M-II concentrations. The pharmacokinetic parameters of plasma omeprazole were unaffected by coadministration with Ramelteon (Reference data 5.3.3.4-5, TL036).

4.(ii).A.(4).6) Rifampicin

Foreign healthy adult subjects (27 subjects included in pharmacokinetic assessment) received a single oral dose of 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) in the morning or 600 mg of oral rifampicin once daily for 11 days plus 32 mg of Ramelteon on Day 11. The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + rifampicin/Ramelteon alone) with their 90% CIs were 0.18 [0.14, 0.23] and 0.19 [0.15, 0.24], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 0.19 [0.17, 0.21] and 0.11 [0.10, 0.12], respectively. Coadministration with rifampicin decreased the exposures to unchanged Ramelteon and M-II (Reference data 5.3.3.4-6, TL035).

4.(ii).A.(4).7) Dextromethorphan

Foreign healthy adult subjects (35 subjects included in pharmacokinetic assessment) received a single oral dose of 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) alone, 30 mg of dextromethorphan alone, or Ramelteon 32 mg plus dextromethorphan 30 mg in the morning in the fasted state. Ramelteon did not significantly interact with dextromethorphan pharmacokinetically (Reference data 5.3.3.4-7, TL026).

4.(ii).A.(4).8) Theophylline

Foreign healthy adult subjects (34 subjects included in pharmacokinetic assessment) were orally administered 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) alone, 300 mg of theophylline alone, or Ramelteon 32 mg plus theophylline 300 mg once daily in the morning in the fasted state for 10 days. The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + theophylline/Ramelteon alone) with their 90% CIs were 1.35 [1.08, 1.70] and 1.40 [1.23, 1.60], respectively, and coadministration with theophylline increased the exposure to unchanged Ramelteon while there were no significant effects on serum M-II concentrations. Plasma theophylline concentrations were not significantly affected by coadministration with Ramelteon (Reference data 5.3.3.4-8, TL027).

4.(ii).A.(4).9) Midazolam

Twenty-eight foreign healthy adult subjects received a single oral dose of 10 mg of midazolam in the morning in the fasted state or 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) once daily in the morning for 10 days (fasted administration on Days 7-10) plus 10 mg of midazolam on Day 10. Midazolam did not significantly affect the pharmacokinetics of Ramelteon (Reference data 5.3.3.4-9, TL024).

4.(ii).A.(4).10) Warfarin

Foreign healthy adult subjects (22 subjects included in pharmacokinetic assessment) received a single oral dose of warfarin (the optimum dose titrated from 1 mg up to 15 mg to achieve prothrombin time within the target range of 1.2-1.7 times higher than the baseline prothrombin time) or warfarin plus 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) once daily for 7 days. Coadministration with Ramelteon had no effects on plasma *R*-warfarin and *S*-warfarin concentrations and no statistically significant differences were found in prothrombin time or INR (International Normalization Ratio) between warfarin administered alone and warfarin administered with Ramelteon (Reference data 5.3.3.4-10, TL033).

4.(ii).A.(4).11) Digoxin

Foreign healthy adult subjects (20 subjects included in pharmacokinetic assessment) received 0.5 mg of digoxin alone or 0.5 mg of digoxin plus 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) in the morning on Day 1, a single oral dose of 0.25 mg of digoxin in the evening on Day 1, and 0.2 mg of digoxin alone or 0.2 mg of digoxin plus 16 mg of Ramelteon once daily in the morning on Days 2 through 12 (after breakfast on Days 1-6, in the fasted state on Days 7-12). The mean ratios of C_{max} and $AUC_{0\text{-}\tau}$ of serum digoxin (digoxin + Ramelteon/digoxin alone) with their 90% CIs were 0.91 [0.79, 1.04] and 0.97 [0.92, 1.02], respectively. The 90% CI for the mean C_{max} ratio fell slightly outside the range of 0.80 to 1.25, which is unlikely to become a clinically relevant problem, because the 90% CI for the mean $AUC_{0\text{-}\tau}$ ratio

fell within the range of 0.80 to 1.25 (Reference data 5.3.3.4-11, TL037).

4.(ii).A.(4).12) Ethanol

Foreign healthy adult subjects (21 subjects included in pharmacokinetic assessment) received a single oral dose of 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) or placebo about 1.5 hours after breakfast and then received 0.6 g/kg of ethanol or placebo in three divided oral doses immediately, 10 minutes later, and 20 minutes later. The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + ethanol/Ramelteon alone) with their 90% CIs were 1.43 [0.94, 2.18] and 1.47 [1.04, 2.07], respectively, and coadministration with ethanol increased the exposure to unchanged Ramelteon, but did not significantly affect serum M-II concentrations. Coadministration with Ramelteon did not affect plasma ethanol concentrations. Concomitant administration of Ramelteon and ethanol compared with ethanol alone had significant effects on psychomotor function (Psychomotor Vigilance Task Test [PVT]), alertness as assessed on a Visual Analog Scale (VAS), and attention (Digit symbol substitution test [DSST]), but did not affect memory function (Hopkins Verbal Learning Test [HVLT]) (Reference data 5.3.3.4-12, TL028).

Twenty-eight foreign healthy adult subjects received a single oral dose of 32 mg of Ramelteon (the phase II/III 32 mg tablet formulation) or placebo about 1.5 hours after breakfast and then received 0.6 g/kg of ethanol or placebo in three divided oral doses immediately, 10 minutes later, and 20 minutes later. Concomitant administration of Ramelteon and ethanol compared with ethanol alone had significant effects on PVT, VAS alertness, and DSST, but did not affect memory function (Delayed Word Recognition [DWR]) (Reference data 5.3.3.4-13, TL043).

4.(ii).A.(4).13) Sertraline (SRT)

Forty-eight foreign healthy adult subjects received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning in the fasted state on Day 1 followed by 13 days of washout and then received 50 mg of oral SRT once daily in the morning in the fasted state on Days 15 through 27 plus 8 mg of Ramelteon on Day 27 (Treatment sequence I), or received a single oral dose of 50 mg of SRT in the morning in the fasted state on Day 1 followed by 13 days of washout and then received 8 mg of Ramelteon once daily in the morning in the fasted state on Days 15 through 27 plus 50 mg of SRT on Day 27 (Treatment sequence II). The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + SRT/Ramelteon alone) with their 90% CIs were 0.57 [0.43, 0.74] and 0.77 [0.62, 0.97], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 0.82 [0.75, 0.90] and 0.98 [0.92, 1.04], respectively, and coadministration with SRT decreased the C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon and the C_{max} of serum M-II. The pharmacokinetic parameters of plasma unchanged SRT and metabolite were not significantly affected by coadministration with Ramelteon (Reference data 5.3.3.4-14, TL050).

4.(ii).A.(4).14) Gabapentin (GBP)

Forty-eight foreign healthy adult subjects received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning in the fasted state on Day 1 followed by 3 days of washout and then received 400 mg of oral GBP 3 times daily on Days 5 through 10 and 8 mg of Ramelteon plus 400 mg of GBP in the morning in the fasted state on Day 11 (Treatment sequence I), or received a single oral dose of 400 mg of GBP in the morning in the fasted state on Day 1 followed by 3 days of washout and then received 8 mg of Ramelteon once daily in the morning in the fasted state on Days 5 through 11 plus 400 mg of GBP in the morning in the fasted state on Day 11 (Treatment sequence II). The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + GBP/Ramelteon alone) with their 90% CIs were 1.27 [1.03, 1.57] and 1.14 [0.93, 1.39], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 0.78 [0.59, 1.05] and 1.01 [0.95, 1.07], respectively. Coadministration with GBP increased serum unchanged Ramelteon concentrations and decreased the C_{max} of serum M-II. The pharmacokinetic parameters of plasma gabapentin were unaffected by coadministration with Ramelteon (Reference data 5.3.3.4-15, TL054).

4.(ii).A.(4).15) Donepezil

Foreign healthy adult subjects (45 subjects included in pharmacokinetic assessment) received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning in the fasted state on Day 1 followed by 3 days of washout and then received oral donepezil (5 mg on Days 5-11, 10 mg on Days 12-27) once daily in the morning in the fasted state on Days 5 through 27 plus 8 mg of Ramelteon on Day 27 (Treatment sequence I), or received a single oral dose of 5 mg of donepezil in the morning in the fasted state on Day 1 followed by 18 days of washout and then received 8 mg of Ramelteon once daily in the morning in the fasted state on Days 20 through 27 plus 5 mg of donepezil on Day 27 (Treatment sequence II). The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + donepezil/Ramelteon alone) with their 90% CIs were 1.87 [1.36, 2.55] and 2.00 [1.45, 2.75], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 0.97 [0.92, 1.03] and 1.07 [1.02, 1.13], respectively. Coadministration with donepezil increased serum unchanged Ramelteon concentrations. The pharmacokinetic parameters of plasma donepezil were unaffected by coadministration with Ramelteon (Reference data 5.3.3.4-16, TL056).

4.(ii).A.(4).16) Zolpidem

Foreign healthy adult subjects (47 subjects included in pharmacokinetic assessment) received a single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) in the morning in the fasted state on Day 1 followed by 3 days of washout and then received 10 mg of oral zolpidem once daily in the morning in the fasted state on Days 5 through 10 and 10 mg of zolpidem plus 8 mg of Ramelteon on Day 11 (Treatment sequence I), or received a single oral dose of 10 mg of zolpidem in the morning in the fasted state on Day 1 followed by 3 days of washout and then received 8 mg of Ramelteon once daily in the morning in the fasted state on Days 5 through 10 and 10 mg of zolpidem plus 8 mg of Ramelteon on Day 11 (Treatment sequence II). The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon (Ramelteon + zolpidem/Ramelteon alone) with their 90% CIs were 1.03 [0.78, 1.36] and 1.09 [0.90, 1.33], respectively, and the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum M-II with their 90% CIs were 0.86 [0.80,

0.92] and 1.00 [0.95, 1.05], respectively. While the 90% CIs for the mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of serum unchanged Ramelteon did not meet the equivalence criteria (0.8-1.25), serum M-II concentrations were unaffected by coadministration with zolpidem. The mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of plasma zolpidem with their 90% CIs were 0.84 [0.77, 0.92] and 0.98 [0.92, 1.04], respectively, and the 90% CI for the mean C_{max} ratio fell slightly outside the equivalence limits (0.8-1.25), which is considered of no clinical relevance (Reference data 5.3.3.4-17, TL070).

4.(ii).A.(5) Special study

4.(ii).A.(5).1) Effects on circadian rhythms

Eighteen foreign healthy adult subjects received a single oral dose of placebo at 17:00 on Days 1 and 3 and a single oral dose of 4 mg or 16 mg of Ramelteon (the phase II/III 4 mg or 16 mg tablet formulation), 5 mg of melatonin, or placebo at 17:00 on Day 2 and the phase shift of the Dim-Light Salivary Melatonin Onset (DLSMO)[15] from Day 1 to Day 3 was assessed. Administration of 4 mg or 16 mg of Ramelteon or melatonin caused a 18.0-, 17.1-, or 22.5-minute phase advance of the DLSMO, respectively, and placebo administration delayed the DLSMO by 18.8 minutes (Reference data 5.3.5.4-11, TL006).

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

4.(ii).B.(1) Gender differences in the pharmacokinetics of Ramelteon

As serum unchanged Ramelteon concentrations tended to be higher in women than in men in a clinical pharmacology study in foreign healthy adult subjects (Reference data 5.3.3.3-2, Study TL003), PMDA asked the applicant to explain gender differences in the pharmacokinetics of Ramelteon and its effects on the efficacy and safety of Ramelteon.

The applicant explained as follows:

The C_{max} and AUC data were pooled from pharmacokinetic studies (other than Study TL003) that enrolled both men and women (Reference data 5.3.3.3-2) (Reference data 5.3.3.1-5, PNFP001; Reference data 5.3.3.1-6, EC002; Reference data 5.3.3.3-3, TL029; Reference data 5.3.3.3-4, TL030; Reference data 5.3.3.4-1, TL007; Reference data 5.3.3.4-2, TL009; Reference data 5.3.3.4-3, TL049; Reference data 5.3.3.4-4, TL034; Reference data 5.3.3.4-5, TL036; Reference data 5.3.3.4-14, TL050; Reference data 5.3.3.4-15, TL054; Reference data 5.3.3.4-16, TL056). Based on the pooled data, the C_{max} and AUC of serum unchanged Ramelteon were about 2-fold higher and the C_{max} and AUC of serum M-II were about 1.2-fold higher in women than in men. As possible causative factors, metabolizing enzymes and body weight were examined for gender differences. As a result, no major gender differences are known for Ramelteon-metabolizing enzymes, i.e. CYP1A2, the CYP2C subfamily, and CYP3A4. Although men had about a 1.1- to 1.3-fold higher body weight than women in all studies, as the differences in body weight were smaller than the differences in serum unchanged Ramelteon concentrations, gender differences in the pharmacokinetics of Ramelteon cannot be accounted for by differences in body weight alone. Some studies showed higher serum unchanged Ramelteon and M-II concentrations in men than in women. Thus, gender differences in the pharmacokinetics of Ramelteon may be due to an inter-individual variability. In a

[15] The first time at which a salivary concentration of melatonin exceeded 4.0 pg/mL.

Japanese phase III study (5.3.5.1-3.1, CCT003), the difference in the subjective sleep latency (sSL) at Week 1 between the Ramelteon and placebo groups (least square mean) tended to be greater in women than in men, i.e. -2.37 minutes in men and -5.81 minutes in women. Meanwhile, no consistent results were obtained across foreign placebo-controlled comparative studies (Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-11, TL025). Among patients treated with the proposed dose of 8 mg of Ramelteon in Japanese clinical studies, the incidence of overall adverse events was 19.2% (94 of 490 subjects) in men and 26.8% (214 of 799 subjects) in women for short-term studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003) and 44.1% (26 of 59 subjects) in men and 39.7% (52 of 131 subjects) in women for a long-term study (5.3.5.2-1.1, OCT002). In foreign clinical studies, the incidence of overall adverse events was 39.9% (184 of 461 subjects) in men and 43.5% (308 of 708 subjects) in women for short-term studies (Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-11, TL025; Reference data 5.3.5.1-12, TL069), and 60.7% (119 of 196 subjects) in men and 62.9% (176 of 280 subjects) in women for long-term studies (5.3.5.1-4, EC302; 5.3.5.2-2, TL022). There were also no marked gender differences in the nature or severity of the observed adverse events. Therefore, gender differences in the pharmacokinetics of Ramelteon will not become a clinically relevant problem.

PMDA considers as follows:
Although gender differences in the pharmacokinetics of Ramelteon have been noted, as no clear gender differences in the efficacy or safety of Ramelteon have been found, gender differences in the pharmacokinetics of Ramelteon are unlikely to become a clinically relevant problem. It is necessary to continue to investigate gender differences in the efficacy and safety of Ramelteon via post-marketing surveillance.

4.(ii).B.(2) Safety in the elderly and special populations (patients with hepatic impairment, patients with renal impairment)
PMDA asked the applicant to explain the safety of Ramelteon in patients with hepatic or renal impairment.

The applicant explained as follows:
In a foreign clinical study in subjects with mild to moderate hepatic impairment (Reference data 5.3.3.3-3, TL029), although the C_{max} and $AUC_{0-\tau}$ of serum unchanged Ramelteon were higher in subjects with hepatic impairment compared with their healthy matched controls[13] (2.5-fold and 3.6-fold higher, respectively, in subjects with mild hepatic impairment; 8.4-fold and 10.7-fold higher, respectively, in subjects with moderate hepatic impairment), the incidence of adverse events was 83.3% (10 of 12 subjects) in subjects with mild hepatic impairment and 75.0% (9 of 12 subjects) in their healthy matched controls[13] and 75.0% (9 of 12 subjects) in subjects with moderate hepatic impairment and 83.3% (10 of 12 subjects) in their healthy matched controls[13], and most events were mild in severity. In Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), patients with hepatic impairment[16] were allowed to be enrolled, and the incidence of adverse events tended to be higher in

[16] "Patients with hepatic disease" were to be excluded from CCT001 and CCT002 and "patients with significant hepatic disease (unless controlled

patients with hepatic impairment in both the Ramelteon and placebo groups, but the difference between the placebo and Ramelteon groups did not significantly differ according to the presence or absence of hepatic impairment (patients with hepatic impairment, 31.6% [6 of 19 subjects] in the placebo group and 48.8% [20 of 41 subjects] in the Ramelteon group; patients with normal hepatic function, 23.3% [211 of 904 subjects] in the placebo group and 34.3% [560 of 1633 subjects] in the Ramelteon group). None of the observed adverse events were specific to patients with hepatic impairment, and most of the observed events were mild in severity and resolved during treatment. According to foreign post-marketing safety information covering the period from July 22, 2005 to September 30, 2009, there were no major differences in the nature of adverse drug reactions according to the presence or absence of concurrent hepatic disease. Based on the above, no dose adjustment is required for patients with mild to moderate hepatic impairment. However, since Ramelteon is metabolized mainly by the liver, Ramelteon should be administered to these patients with caution. Therefore, patients with mild to moderate hepatic impairment have been listed in the "Careful Administration" section of the package insert, and Ramelteon has been contraindicated in patients with severe hepatic impairment as the efficacy and safety of Ramelteon in such patients have not been established.

Then, the applicant explained the following (a) to (d) and claimed that no dose adjustment is required for patients with renal impairment:

(a) In a mass balance study using ^{14}C-Ramelteon (Reference data 5.3.3.1-4, EC004), the primary metabolites in the urine were M-VIII and its glucuronate conjugate. M-VIII was detected also in rat and monkey urine. In a rat 13-week dose range-finding study for a carcinogenicity study (4.2.3.4.1-5), pathological findings such as basophilic renal tubules were observed at doses ≥150 mg/kg/day. However, no renal toxicity findings were noted in the monkey. The M-VIII glucuronide was not detected in the urine of any animal species, but is unlikely to become a toxicological problem because it is highly water-soluble and is an ether glucuronide and is unlikely to react with and covalently bind to the biological component.

(b) In a clinical study in subjects with renal impairment (Reference data 5.3.3.3-4, TL030), the C_{max} and $AUC_{0-\tau}$ of serum unchanged Ramelteon varied considerably and it was difficult to compare the data between subjects with renal impairment and their healthy matched controls,[14)] but the renal clearance of Ramelteon was not significantly affected by the degree of renal impairment.

(c) In Japanese placebo-controlled studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), patients with non-serious renal impairment were allowed to be enrolled and the incidence of adverse events among patients with renal impairment was 25.0% (2 of 8 subjects) in the placebo group and 34.8% (8 of 23 subjects) in the Ramelteon group, which were not significantly different from 23.5% (215 of 915 subjects) in the placebo group and 34.6% (572 of 1651 subjects) in the Ramelteon group among patients with normal renal function. Though in a limited number of cases, there were no major differences in the incidence or severity of adverse events according to the degree of renal impairment.

(d) According to foreign post-marketing safety information covering the period from July 22, 2005 to September 30, 2009, there were no major differences in the nature of adverse drug reactions based on

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and stable with protocol-allowed medication at least 30 days prior to the start of the lead-in period) were to be excluded from CCT003.

the presence or absence of renal disease.

As the C_{max} and AUC of serum unchanged Ramelteon were higher in elderly subjects than in non-elderly subjects in a clinical study involving Japanese healthy adult and elderly subjects (5.3.3.3-1, CPH005), PMDA asked the applicant to explain whether dose adjustment is required for the elderly and whether a caution should be provided.

The applicant explained as follows:
In Japanese and foreign clinical studies that assessed the effect of age on the pharmacokinetics of Ramelteon (5.3.3.3-1, CPH005; Reference data 5.3.3.3-2, TL003), serum unchanged Ramelteon and M-II concentrations at a dose of 16 mg of Ramelteon were higher in elderly subjects than in non-elderly subjects. However, in Japanese placebo-controlled studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003), the incidence of adverse events among non-elderly subjects was 24.0% (193 of 805 subjects) in the placebo group and 36.1% (504 of 1395 subjects) in the Ramelteon group. The incidence of adverse events among elderly subjects was 20.3% (24 of 118 subjects) in the placebo group and 27.2% (76 of 279 subjects) in the Ramelteon group. The incidence of adverse events was not increased in elderly subjects and none of the adverse events were specific to elderly subjects. Therefore, there is no major problem with the safety of Ramelteon in the elderly and no dose adjustment is required. Meanwhile, as the elderly often has reduced physiological function, the package insert will recommend careful administration in the elderly.

PMDA considers as follows:
At present, there is no major problem with the above response (Ramelteon is contraindicated in patients with severe hepatic impairment; patients with mild to moderate hepatic impairment and the elderly are listed in the “Careful Administration” section of the package insert; and no dose adjustment is recommended for patients with mild to moderate hepatic impairment and the elderly). However, as the number of subjects studied was small and the information is limited, the efficacy and safety of Ramelteon in the elderly and special populations (patients with hepatic or renal impairment) need to be further investigated via post-marketing surveillance.

4.(ii).B.(3) Drug-drug interactions
PMDA asked the applicant to explain about drugs that potentially interact with Ramelteon.

The applicant explained as follows:
Ramelteon is metabolized mainly by CYP1A2, CYP3A4, and the CYP2C subfamily and a drug-drug interaction study showed that coadministration with a CYP1A2 inhibitor, fluvoxamine (FLV), markedly increased serum unchanged Ramelteon and M-II concentrations. Thus, concomitant use with FLV has been contraindicated. The results of interaction studies using human hepatic microsomes (4.2.2.6-1, 4.2.2.6-2) indicated that the effects of other CYP1A2 inhibitors on the metabolism of Ramelteon are not significant. However, as no drug-drug interaction studies in humans have been conducted and it is anticipated that coadministration with a potent CYP1A2 inhibitor increases Ramelteon exposure, CYP1A2 inhibitors have been listed in the “Precautions for coadministration” section of the package insert. Furthermore, as

coadministration with a potent CYP inducer, rifampicin, markedly decreased serum unchanged Ramelteon and M-II concentrations, which raised a concern about the efficacy of Ramelteon, CYP inducers have been listed in the "Precautions for coadministration" section of the package insert. As coadministration with ethanol increased serum unchanged Ramelteon concentrations and there were also pharmacodynamic effects, alcohol has been listed in the "Precautions for coadministration" section of the package insert. Besides the above-mentioned drugs, drug-drug interaction studies of Ramelteon with ketoconazole, fluconazole, fluoxetine, omeprazole, dextromethorphan, theophylline, gabapentin, sertraline, donepezil, or zolpidem showed that the C_{max} or AUC of serum unchanged Ramelteon or M-II was affected. However, when the total active compound concentrations were determined from the relative potency of unchanged Ramelteon to the active metabolite (M-II), there were no significant effects on blood drug concentrations. There was no major problem with the tolerability of Ramelteon in combination with these drugs and the tolerability of Ramelteon at doses up to 32 mg was demonstrated in a clinical study in Japanese healthy adult subjects (5.3.3.1-3, CPH006) and a phase II study (5.3.5.1-1, CCT001), etc. Therefore, interactions with these drugs are unlikely to become a clinically relevant problem. However, as the US package insert states that Ramelteon should be administered with caution in patients taking ketoconazole or fluconazole, these drugs have been listed in the "Precautions for coadministration" section of the Japanese package insert as well.

As smoking is known to induce CYP1A2 activity, PMDA asked the applicant to explain the effect of smoking on the efficacy and safety of Ramelteon.

The applicant explained as follows:
In Japanese and foreign clinical studies (Japan, 5.3.3.1-1, CPH001 and 5.3.3.1-3, CPH006; Overseas, Reference data 5.3.3.3-3, TL029), the pharmacokinetic parameters following a single oral dose of Ramelteon were evaluated by smoking status. As a result, there was a large variability in serum unchanged Ramelteon concentrations and it was difficult to evaluate the effect of smoking. However, the distribution of individual subjects overlapped and there were no major differences in the C_{max} or AUC of serum M-II, a metabolite formed by CYP1A2, according to smoking status. In Japanese and foreign clinical studies (Japan, 5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; Overseas, Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-11, TL025), there was no consistent trend in the effect of smoking on the efficacy of Ramelteon across the studies. Also regarding safety, the incidence of adverse events in Japanese placebo-controlled comparative studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003) was 24.6% (43 of 175 subjects) in the placebo group and 38.1% (175 of 459 subjects) in the Ramelteon group among smokers and 23.3% (174 of 748 subjects) in the placebo group and 33.3% (405 of 1215 subjects) in the Ramelteon group among non-smokers. In foreign placebo-controlled comparative studies (Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-11, TL025), the incidence of adverse events was 54.3% (44 of 81 subjects) in the placebo group and 57.1% (112 of 196 subjects) in the Ramelteon group among smokers and 42.5% (347 of 816 subjects) in the placebo group and 50.7% (712 of 1403 subjects) in the Ramelteon group among non-smokers. There were also no major differences in the nature or severity of the observed adverse events. Therefore, smoking is

unlikely to significantly affect the efficacy and safety of Ramelteon.

PMDA considers as follows:
Taking account of the results of a drug-drug interaction study with fluvoxamine (Reference data 5.3.3.4-3)etc., it is appropriate to contraindicate concomitant use with fluvoxamine. Regarding the safety of concomitant use with other CYP1A2 inhibitors, adequate caution should be exercised when Ramelteon is used with other CYP1A2 inhibitors; a caution should be provided in the package insert, an investigation should be conducted via post-marketing surveillance, and the obtained information should be transmitted to the medical practice appropriately. As for the effects of other concomitant drugs and smoking, the applicant's explanation poses no particular problem at present and is acceptable, but it is necessary to continue to investigate via post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from 4 Japanese clinical studies in patients with insomnia (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; 5.3.5.2-1.1, OCT002) were submitted. As the safety evaluation data, the results from Japanese phase I studies in healthy adult subjects (5.3.1.1-2, CPH007; 5.3.3.1-1, CPH001; 5.3.3.1-2, CPH002; 5.3.3.1-3, CPH006; 5.3.3.3-1, CPH005; 5.3.5.4-13, CPH003) were submitted. The results from foreign clinical studies were also submitted as the evaluation data or the reference data.

4.(iii).A.(1) Clinical pharmacology studies

4.(iii).A.(1).1) Human pharmacokinetic study (5.3.1.1-2, CPH007 [20 to 20])

An open-label, crossover, comparative study was conducted to assess the effect of food on the safety and pharmacokinetics of Ramelteon in Japanese healthy adult male subjects (Target sample size of 20, 10 subjects per group) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods"].

A single oral dose of 8 mg of Ramelteon (the proposed commercial formulation) was to be administered in the morning in the fasted state or after breakfast. The washout period was 14 days.

All of 20 treated subjects were included in the safety analysis.

The incidence of adverse events (including laboratory test abnormalities) was 60.0% (12 of 20 subjects) after fasted administration and 65.0% (13 of 20 subjects) after fed administration and no deaths or other serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 50.0% (10 of 20 subjects) after fasted administration and 65.0% (13 of 20 subjects) after fed administration and the main adverse events were somnolence (10 subjects after fasted administration, 13 subjects after fed administration) etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate).

Based on the above, the applicant explained that there should be no major problem with the safety of a single dose of 8 mg of Ramelteon administered to healthy adult male subjects in the morning in the fasted state or after breakfast.

4.(iii).A.(1).2) Single-dose study (5.3.3.1-1, CPH001 [19 to 19])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to assess the safety and pharmacokinetics of a single oral dose of Ramelteon and food effect in Japanese healthy adult male subjects (Target sample size of 48, 12 subjects for each step [8 subjects in the Ramelteon group and 4 subjects in the placebo group], a total of 84 subjects) [for pharmacokinetics, see "4.(ii) Summary of clinical pharmacology studies"].

A single oral dose of Ramelteon (the phase I 0.1 mg, 1 mg, and 4 mg tablet formulations) at doses of 0.3 mg (Step 1), 1 mg (Step 2), 2 mg (Step 3), 4 mg (Step 4), 8 mg (Step 5), or 16 mg (Step 6) or placebo was to be administered in the morning in the fasted state and a single oral dose was to be administered also after breakfast in Step 5. The subjects assigned to Step 1 were the same as those assigned to Step 3, the subjects assigned to Step 2 were the same as those assigned to Step 4, and the subjects assigned to Step 5 were studied in both fasted and fed states.

All of 50 treated subjects (a total of 84 subjects) were included in the safety analysis.

After fasted administration, the incidence of adverse events (including laboratory test abnormalities) was 70.8% (17 of 24 subjects) in the placebo group, 75.0% (6 of 8 subjects) in the Ramelteon 0.3 mg group, 100.0% (8 of 8 subjects) in the Ramelteon 1 mg group, 100.0% (8 of 8 subjects) in the Ramelteon 2 mg group, 75.0% (6 of 8 subjects) in the Ramelteon 4 mg group, 62.5% (5 of 8 subjects) in the Ramelteon 8 mg group, and 87.5% (7 of 8 subjects) in the Ramelteon 16 mg group. After fed administration, the incidence of adverse events (including laboratory test abnormalities) was 100.0% (4 of 4 subjects) in the placebo group and 75.0% (6 of 8 subjects) in the Ramelteon 8 mg group. No deaths or other serious adverse events were reported.

After fasted administration, the incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 62.5% (15 of 24 subjects) in the placebo group, 75.0% (6 of 8 subjects) in the Ramelteon 0.3 mg group, 100.0% (8 of 8 subjects) in the Ramelteon 1 mg group, 87.5% (7 of 8 subjects) in the Ramelteon 2 mg group, 75.0% (6 of 8 subjects) in the Ramelteon 4 mg group, 62.5% (5 of 8 subjects) in the Ramelteon 8 mg group, and 87.5% (7 of 8 subjects) in the Ramelteon 16 mg group. After fed administration, the incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 100.0% (4 of 4 subjects) in the placebo group and 75.0% (6 of 8 subjects) in the Ramelteon 8 mg group. After fasted administration, the main adverse events were sleepiness (10 subjects in the placebo group, 5 subjects in the

Ramelteon 0.3 mg group, 7 subjects in the Ramelteon 1 mg group, 5 subjects in the Ramelteon 2 mg group, 4 subjects in the Ramelteon 4 mg group, 5 subjects in the Ramelteon 8 mg group, 6 subjects in the Ramelteon 16 mg group), balance disorder (2 subjects in the placebo group, 1 subject in the Ramelteon 0.3 mg group, 2 subjects in the Ramelteon 1 mg group, 2 subjects in the Ramelteon 2 mg group, 1 subject in the Ramelteon 4 mg group, 0 subject in the Ramelteon 8 mg group, 1 subject in the Ramelteon 16 mg group), mental dullness (6 subjects in the placebo group, 1 subject in the Ramelteon 0.3 mg group, 1 subject in the Ramelteon 1 mg group, 3 subjects in the Ramelteon 2 mg group, 0 subject in the Ramelteon 4 mg group, 1 subject in the Ramelteon 8 mg group, 0 subject in the Ramelteon 16 mg group), and wave slowing (1 subject in the placebo group, 1 subject in the Ramelteon 0.3 mg group, 1 subject in the Ramelteon 1 mg group, 1 subject in the Ramelteon 2 mg group, 1 subject in the Ramelteon 4 mg group, 1 subject in the Ramelteon 8 mg group, 1 subject in the Ramelteon 16 mg group) etc. After fed administration, the main adverse events were sleepiness (3 subjects in the placebo group, 6 subjects in the Ramelteon 8 mg group) and balance disorder (1 subject in the placebo group, 1 subject in the Ramelteon 8 mg group) etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate) or ECG.

Based on the above, the applicant explained that there should be no major problem with the safety of a single dose of 0.3 to 16 mg of Ramelteon in healthy adult male subjects.

4.(iii).A.(1).3) Multiple-dose study (5.3.3.1-2, CPH002 [[redacted] 19[redacted] to [redacted] 19[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to assess the safety and pharmacokinetics of multiple oral doses of Ramelteon in Japanese healthy adult male subjects (Target sample size of 24, 12 subjects for each step [8 subjects in the Ramelteon group and 4 subjects in the placebo group]) [for pharmacokinetics, see "4.(ii) Summary of clinical pharmacology studies"].

Ramelteon (the phase I 4 mg tablet formulation) 8 mg or placebo in Step 1 and Ramelteon 16 mg or placebo in Step 2 were to be orally administered once daily 2 hours prior to bedtime. The duration of treatment was 7 days.

All of 24 treated subjects (8 subjects each in the placebo, Ramelteon 8 mg, and Ramelteon 16 mg groups) were included in the safety analysis.

The incidence of adverse events (including laboratory test abnormalities) was 100.0% (8 of 8 subjects) in all three groups. No deaths or other serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 87.5% (7 of 8 subjects) in the placebo group, 100.0% (8 of 8 subjects) in the Ramelteon 8 mg group, and 100.0% (8 of 8 subjects) in the Ramelteon 16 mg group, and the main adverse events were sleepiness (7 subjects in the placebo group, 8 subjects in the Ramelteon 8 mg group, 8

subjects in the Ramelteon 16 mg group), balance disorder (1 subject in the placebo group, 2 subjects in the Ramelteon 8 mg group, 1 subject in the Ramelteon 16 mg group), malaise (1 subject in the placebo group, 1 subject in the Ramelteon 8 mg group, 1 subject in the Ramelteon 16 mg group), etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate) or ECG.

Based on the above, the applicant explained that there should be no major problem with the safety of once-daily administration of Ramelteon at 8 or 16 mg for 7 days in healthy adult male subjects.

4.(iii).A.(1).4) Single- and multiple-dose study at high dose (5.3.3.1-3, CPH006 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, double-blind, parallel-group, comparative study was conducted to assess the safety and pharmacokinetics of single and multiple oral doses of Ramelteon in Japanese healthy adult male subjects (Target sample size of 24, 12 subjects for each step [8 subjects in the Ramelteon group and 4 subjects in the placebo group]) [for pharmacokinetics, see "4.(ii) Summary of clinical pharmacology studies"].

In Step 1, a single oral dose of 32 mg of Ramelteon (the phase I 1 mg and 10 mg tablet formulations) or placebo was to be administered in the morning in the fasted state. In Step 2, 32 mg of Ramelteon or placebo was to be orally administered once daily 3 hours after the evening meal for 7 days.

All of 24 treated subjects (4 subjects in the placebo group and 8 subjects in the Ramelteon group for each step) were included in the safety analysis.

The incidence of adverse events (including laboratory test abnormalities) was 25.0% (1 of 4 subjects) in the placebo group and 87.5% (7 of 8 subjects) in the Ramelteon group in Step 1 and 100.0% (4 of 4 subjects) in the placebo group and 87.5% (7 of 8 subjects) in the Ramelteon group in Step 2. No deaths or other serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 0.0% (0 of 4 subjects) in the placebo group and 75.0% (6 of 8 subjects) in the Ramelteon group in Step 1, and 75.0% (3 of 4 subjects) in the placebo group and 87.5% (7 of 8 subjects) in the Ramelteon group in Step 2. The main adverse events were sleepiness (Step 1, 0 subject in the placebo group and 4 subjects in the Ramelteon group; Step 2, 2 subjects in the placebo group and 5 subjects in the Ramelteon group) etc. in both steps.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate). ECG revealed supraventricular extrasystoles in 1 subject of the Ramelteon group in Step 1, but its causal relationship to study drug was denied, and there were no other clinically significant changes.

Based on the above, the applicant explained that there should be no major problem with the safety of 32 mg

of Ramelteon administered as a single dose or once daily for 7 days in healthy adult male subjects.

4.(iii).A.(1).5) Single-dose pharmacokinetic study in the elderly (5.3.3.3-1, CPH005 [20 to 20])

An open-label study was conducted to assess the safety and pharmacokinetics of a single oral dose of Ramelteon in Japanese healthy elderly and younger adult (non-elderly) male subjects (Target sample size of 24, 12 subjects per group) [for pharmacokinetics, see "4.(ii) Summary of clinical pharmacology studies"].

Subjects were to receive a single oral dose of 16 mg of Ramelteon (the phase II/III 16 mg tablet formulation) 90 minutes after breakfast.

All of 24 treated subjects (12 elderly subjects and 12 non-elderly subjects) were included in the safety analysis.

The incidence of adverse events (including laboratory test abnormalities) was 58.3% (7 of 12 subjects) in the elderly group and 75.0% (9 of 12 subjects) in the non-elderly group. No deaths or other serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 58.3% (7 of 12 subjects) in the elderly group and 66.7% (8 of 12 subjects) in the non-elderly group. The main adverse events were sleepiness (4 elderly subjects, 7 non-elderly subjects) and headache (2 elderly subjects, 0 non-elderly subject) etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate) or ECG.

Based on the above, the applicant explained that there should be no major problem with the safety of a single dose of 16 mg of Ramelteon in elderly and non-elderly subjects.

4.(iii).A.(1).6) PSG phase I study (5.3.5.4-13, CPH003 [20 to 20])

A placebo-controlled, randomized, double-blind, crossover, comparative study (3 treatments × 3 periods) was conducted to assess the effect of Ramelteon on sleep and the safety of Ramelteon in Japanese healthy adult male subjects (Target sample size of 12).

On the first night (Day 1 of hospitalization) for adaptation, a single oral dose of placebo was to be administered 30 minutes prior to bedtime. During the double-blind phase (Days 2-4 of hospitalization), placebo or 8 or 32 mg of Ramelteon (the phase I 8 mg tablet formulation) was to be orally administered once daily 30 minutes prior to bedtime. A 10-day washout period was included between the treatment periods.

All of 12 treated subjects were included in the safety analysis, of whom 11 subjects were included in the pharmacodynamic analysis. Excluded was 1 subject who withdrew consent during the study.

The primary endpoint of the latency to persistent sleep (LPS) as measured by polysomnography (PSG) was as shown in the following table and there were no statistically significant differences in LPS on Days 2 and 4 of hospitalization between any dose of Ramelteon and placebo.

Table. LPS as measured by PSG in Japanese healthy adult subjects (minutes)

		Placebo	Ramelteon 8 mg	Ramelteon 32 mg	*P*-value[a)]
Day 2 of hospitalization	Mean ± SD	12.49 ± 10.86	7.79 ± 8.22	7.21 ± 6.58	0.2169
	Least square mean	12.44	7.68	7.37	
	P-value[b)]	-	0.1436	0.1210	
Day 4 of hospitalization	Mean ± SD	11.27 ± 8.03	12.03 ± 11.18	10.64 ± 8.02	0.9497
	Least square mean	11.39	11.84	10.72	
	P-value[b)]	-	0.8989	0.8507	

a) Analysis of variance (ANOVA) with treatment (dose) and period as factors
b) Pair-wise comparisons with placebo

The incidence of adverse events (including laboratory test abnormalities) was 36.4% (4 of 11 subjects) with placebo, 50.0% (6 of 12 subjects) with 8 mg of Ramelteon, and 54.5% (6 of 11 subjects) with 32 mg of Ramelteon. No deaths or serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 27.3% (3 of 11 subjects) with placebo, 33.3% (4 of 12 subjects) with 8 mg of Ramelteon, and 54.5% (6 of 11 subjects) with 32 mg of Ramelteon. The main adverse events were sleepiness (1 subject when treated with placebo, 3 subjects when treated with 8 mg of Ramelteon, 4 subjects when treated with 32 mg of Ramelteon) etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate) or ECG.

Based on the above, the applicant explained that when 8 or 32 mg of Ramelteon was administered once daily for 3 days to healthy adult subjects, there were no statistically significant differences in LPS as measured by PSG between Ramelteon and placebo, but there should be no major problem with the safety of Ramelteon.

4.(iii).A.(2) Phase II study

4.(iii).A.(2).1) PSG dose-response study (5.3.5.1-1, CCT001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, crossover, comparative study (5 treatments × 5 periods) was conducted to evaluate the efficacy and safety of Ramelteon in patients with chronic insomnia[17] (Target sample size of 60).

Placebo was to be orally administered once daily 30 minutes prior to bedtime for 2 days and then Ramelteon (the proposed commercial formulation and the phase II/III 4 mg, 16 mg, and 32 mg tablet formulations) at doses of 4, 8, 16, or 32 mg or placebo was to be orally administered once daily 30 minutes prior to bedtime for 2 days. A 5-to-12-day washout period was included between the treatment periods.

All of 65 treated subjects (61 subjects treated with placebo, 62 subjects treated with 4 mg of Ramelteon, 61 subjects treated with 8 mg of Ramelteon, 63 subjects treated with 16 mg of Ramelteon, 63 subjects treated with 32 mg of Ramelteon) were included in the Full Analysis Set (FAS) and analyzed for efficacy and safety.

The primary endpoint of the latency to persistent sleep (LPS) as measured by PSG in the FAS was as shown in the following table, and 8 mg and 32 mg of Ramelteon statistically significantly reduced LPS compared with placebo (P = 0.0204 and P = 0.0065, respectively, a mixed effect model with treatment [dose], period, sequence, and carryover as fixed effects and subject as a random effect [Dunnett's multiple comparison procedure]) and a dose-response relationship was observed (P = 0.0046, ANOVA with contrast coefficients of [2, 1, 0, -1, -2]).

Table. LPS as measured by PSG (mean of values on Days 1 and 2 of each period) (FAS)

	Placebo	Ramelteon 4 mg	Ramelteon 8 mg	Ramelteon 16 mg	Ramelteon 32 mg	*P*-value [a) c)]
N	61	62	61	63	63	0.0046
LPS (minutes)	36.03 ± 5.14	29.50 ± 3.26	22.52 ± 2.34	28.97 ± 3.51	24.99 ± 4.06	
Difference from placebo	-	-6.53	-13.51	-7.06	-11.04	
P-value [a) b)]	-	0.2738	0.0204	0.2323	0.0065	

Least square mean ± SE

a) A mixed effect model with treatment (dose), period, sequence, and carryover as fixed effects and subject as a random effect

b) Pairwise comparisons with placebo (Dunnett's multiple comparison procedure)

c) ANOVA with contrast coefficients of [2, 1, 0, -1, -2]

The secondary endpoint of subjective sleep latency (sSL) as determined by post-sleep questionnaire (minutes, least square mean ± SE) was 51.65 ± 5.78 with placebo, 52.32 ± 5.77 with 4 mg of Ramelteon, 40.02 ± 3.99 with 8 mg of Ramelteon, 45.50 ± 4.50 with 16 mg of Ramelteon, and 48.98 ± 6.12 with 32 mg of Ramelteon and no statistically significant differences from placebo were found with any Ramelteon dose, and no dose-response relationship was observed (P = 0.1972, ANOVA with contrast coefficients of [2, 1, 0, -1, -2]).

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17) Patients who were diagnosed with primary insomnia (DSM-IV) and met the following criteria.

1) Subjective sleep latency ≥30 minutes, total sleep time <6.5 hours, and daytime complaints associated with disturbed sleep for at least 3 months

2) Mean LPS ≥20 minutes on 2 consecutive PSG screening nights, with neither night less than 15 minutes and mean wake time ≥60 minutes on 2 consecutive PSG screening nights, with neither night less than 45 minutes

3) Habitual bedtime between 8:30 p.m. and 12:00 a.m.

The incidence of adverse events (including laboratory test abnormalities) was 18.0% (11 of 61 subjects) with placebo, 12.9% (8 of 62 subjects) with 4 mg of Ramelteon, 18.0% (11 of 61 subjects) with 8 mg of Ramelteon, 28.6% (18 of 63 subjects) with 16 mg of Ramelteon, and 27.0% (17 of 63 subjects) with 32 mg of Ramelteon. No deaths or other serious adverse events were reported.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 8.2% (5 of 61 subjects) with placebo, 8.1% (5 of 62 subjects) with 4 mg of Ramelteon, 11.5% (7 of 61 subjects) with 8 mg of Ramelteon, 23.8% (15 of 63 subjects) with 16 mg of Ramelteon, and 20.6% (13 of 63 subjects) with 32 mg of Ramelteon. The main adverse events were somnolence (2 subjects when treated with placebo, 2 subjects when treated with 4 mg of Ramelteon, 3 subjects when treated with 8 mg of Ramelteon, 6 subjects when treated with 16 mg of Ramelteon, 8 subjects when treated with 32 mg of Ramelteon), headache NOS (1 subject when treated with placebo, 0 subject when treated with 4 mg of Ramelteon, 3 subjects when treated with 8 mg of Ramelteon, 4 subjects when treated with 16 mg of Ramelteon, 0 subject when treated with 32 mg of Ramelteon), malaise (1 subject when treated with placebo, 0 subject when treated with 4 mg of Ramelteon, 1 subject when treated with 8 mg of Ramelteon, 4 subjects when treated with 16 mg of Ramelteon, 1 subject when treated with 32 mg of Ramelteon), and dizziness (0 subject when treated with placebo, 1 subject when treated with 4 mg of Ramelteon, 1 subject when treated with 8 mg of Ramelteon, 0 subject when treated with 16 mg of Ramelteon, 2 subjects when treated with 32 mg of Ramelteon) etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate, respiratory rate) or ECG.

Based on the above, the applicant explained that LPS as measured by PSG showed a statistically significant dose-response relationship for 4 to 32 mg of Ramelteon and there was also no major problem with the safety of Ramelteon.

4.(iii).A.(3) Phase II/III study (5.3.5.1-2.1, CCT002 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to evaluate the efficacy and safety of Ramelteon in patients with chronic insomnia[18] (Target sample size of 1083, 361 subjects per group).

During the lead-in period, placebo was to be orally administered once daily 30 minutes prior to bedtime for

[18] Patients who were diagnosed with primary insomnia (DSM-IV) and met the following criteria.

First screening phase (at the start of the lead-in period):

1) Daytime complaints associated with disturbed sleep for at least 3 months

2) Subjective sleep latency ≥60 minutes and total sleep time <6.5 hours

3) Habitual bedtime between 9:00 p.m. and 1:00 a.m.

Second screening phase (at the end of the lead-in period):

Subjective sleep latency ≥45 minutes on at least 3 nights of the lead-in period and the difference between the earliest and latest bedtimes during the lead-in period ≤2 hours

7 days. Then, during the double-blind period, placebo (group L) or 4 mg (group M) or 8 mg (group H) of Ramelteon (the phase II/III 4 mg tablet formulation) was to be orally administered once daily 30 minutes prior to bedtime on Days 1 to 14 and 4 mg (group L), 8 mg (group M), or 16 mg (group H) of Ramelteon was to be orally administered once daily 30 minutes prior to bedtime on Days 15 to 28.

Among a total of 1143 treated subjects (383 subjects in the group L, 375 subjects in the group M, 385 subjects in the group H), 1130 subjects (380 subjects in the group L, 372 subjects in the group M, 378 subjects in the group H) were included in the FAS and analyzed for efficacy and safety. Excluded were 13 subjects who registered at more than one medical institution (3 subjects in the group L, 3 subjects in the group M, 7 subjects in the group H).

The primary endpoint of subjective sleep latency (sSL) over the first week of double-blind treatment (mean of values from Day 1 to Day 7) in the FAS was as shown in the following table. There was no statistically significant difference between the placebo and Ramelteon 8 mg groups. An exploratory comparison showed no statistically significant difference between the placebo and Ramelteon 4 mg groups.

Table. sSL at Week 1 (minutes) (FAS)

Treatment group	N	sSL		Difference from placebo[b)]		
		Lead-in period	Week 1	Difference	95% CI	*P*-value[a)]
Placebo	380	79.86 ± 42.35	64.27 ± 37.18	-	-	-
Ramelteon 4 mg	372	83.28 ± 44.84	64.80 ± 42.51	0.16	[-3.44, 3.76]	0.9315
Ramelteon 8 mg	378	77.46 ± 44.30	59.51 ± 38.57	-3.10	[-6.68, 0.49]	0.0905

Mean ± SD

a) Baseline (mean of values from Day -7 to Day -1)

b) Analysis of covariance (ANCOVA) with baseline as a covariate and treatment as a factor

The incidence of adverse events (including laboratory test abnormalities) was 28.2% (107 of 380 subjects) in the group L (placebo), 26.1% (97 of 372 subjects) in the group M (4 mg), and 25.9% (98 of 378 subjects) in the group H (8 mg) during Days 1 to 14, and 27.0% (100 of 370 subjects) in the group L (4 mg), 23.8% (86 of 361 subjects) in the group M (8 mg), and 22.7% (82 of 362 subjects) in the group H (16 mg) during Days 15 to 28. No deaths were reported. Other serious adverse events were reported by 2 subjects in the group L (suppurative cholangitis and humerus fracture, one case each), 2 subjects in the group M (viral infection and Meniere's disease, one case each), and 3 subjects in the group H (diverticulitis, benign nasopharyngeal neoplasm, and road traffic accident, one case each), but a causal relationship to study drug was denied for all events.

The incidence of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied was 7.1% (27 of 380 subjects) in the group L (placebo), 8.1% (30 of 372 subjects) in the group M (4 mg), and 7.4% (28 of 378 subjects) in the group H (8 mg) during Days 1 to 14, and 7.0% (26 of 370 subjects) in the group L (4 mg), 2.8% (10 of 361 subjects) in the group M (8 mg), and 6.6% (24 of 362 subjects) in the group H (16 mg) during Days 15 to 28. The main adverse events were somnolence (6 subjects in the group L, 11 subjects in the group M, 12 subjects in the group H) and headache (3 subjects in the group L, 2 subjects in the group M, 4 subjects in the group H) etc. during Days 1 to 14, and somnolence (7 subjects in the group L, 2 subjects in the group M, 4 subjects in the group H), headache (2 subjects in the group L, 0 subject in the group M, 3 subjects in the group H), and blood triglycerides increased (3 subjects in the group L, 2 subjects in the group M, 0 subject in the group H) etc.

during Days 15 to 28.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate) or ECG.

Based on the above, the applicant explained that although there was no statistically significant difference in sSL at Week 1 between either 4 mg or 8 mg of Ramelteon and placebo, 8 mg of Ramelteon tended to reduce sSL compared with placebo and there should be no major problem with the safety of Ramelteon.

4.(iii).A. (4) Phase III study (5.3.5.1-3.1, CCT003 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to evaluate the efficacy and safety of Ramelteon in patients with chronic insomnia[19] (Target sample size of 880, 440 subjects per group).

During the lead-in period, placebo was to be orally administered once daily 30 minutes prior to bedtime for 7 days. Then, during the double-blind period, 8 mg of Ramelteon or placebo was to be orally administered once daily 30 minutes prior to bedtime for 14 days.

Among a total of 987 treated subjects (495 subjects in the Ramelteon group, 492 subjects in the placebo group), 971 subjects (489 subjects in the Ramelteon group, 482 subjects in the placebo group) were included in the FAS and analyzed for efficacy and safety. Excluded were 16 subjects who registered at more than one medical institution (6 subjects in the Ramelteon group, 10 subjects in the placebo group).

The primary endpoint of sSL over the first week of double-blind treatment (mean of values from Day 1 to Day 7) in the FAS was as shown in the following table. The difference between Ramelteon and placebo groups with its 95% CI was -4.54 [-7.23, -1.85], and Ramelteon statistically significantly reduced sSL (P = 0.0010, ANCOVA with baseline as a covariate and treatment as a factor). The secondary endpoint of sSL over the second week of double-blind treatment in the FAS was as shown in the following table, and there was no statistically significant difference between the Ramelteon and placebo groups (P = 0.1093, ANCOVA with baseline as a covariate and treatment as a factor).

[19] Patients who were diagnosed with primary insomnia (DSM-IV) and met the following criteria.

First screening phase (at the start of the lead-in period):

1) Daytime complaints associated with disturbed sleep for at least 3 months

2) Subjective sleep latency ≥60 minutes and total sleep time <6.5 hours

3) Habitual bedtime between 9:00 p.m. and 1:00 a.m.

Second screening phase (at the end of the lead-in period):

1) The difference between the earliest and latest bedtimes during the lead-in period ≤2 hours and subjective sleep latency ≥45 minutes on at least 3 nights of the lead-in period

2) The difference of the average subjective sleep latency from the first 3 days to the last 3 days of the lead-in period was within ±30 minutes.

Table. sSL at Week 1 and Week 2 (minutes) (FAS)

		Placebo	Ramelteon	Difference from placebo[b] [95% CI]	*P*-value[b]
Lead-in period	N	482	489	-	-
	sSL[a]	77.42 ± 30.22	77.13 ± 30.81		
Week 1	N	481	489	-4.54 [-7.23, -1.85]	0.0010
	sSL	65.77 ± 30.36	61.07 ± 30.65		
Week 2	N	478	478	-2.36 [-5.25, 0.53]	0.1093
	sSL	59.62 ± 29.13	56.95 ± 31.37		

Mean ± SD
a) Baseline (mean of values from Day -7 to Day -1)
b) ANCOVA with baseline as a covariate and treatment as a factor

Adverse events (including laboratory test abnormalities) occurred in 26.4% (129 of 489 subjects) of the Ramelteon group and 20.5% (99 of 482 subjects) of the placebo group. No deaths were reported. Other serious adverse event was reported by 1 subject of the Ramelteon group (road traffic accident), but its causal relationship to study drug was denied.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 7.8% (38 of 489 subjects) of the Ramelteon group and 7.1% (34 of 482 subjects) of the placebo group. The main adverse events were somnolence (15 subjects in the Ramelteon group, 4 subjects in the placebo group), headache (3 subjects in the Ramelteon group, 3 subjects in the placebo group), blood uric acid increased (3 subjects in the Ramelteon group, 1 subject in the placebo group), dizziness (3 subjects in the Ramelteon group, 0 subject in the placebo group), malaise (3 subjects in the Ramelteon group, 0 subject in the placebo group), etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate).

Based on the above, the applicant explained that the superiority of 8 mg of Ramelteon to placebo in patients with chronic insomnia was demonstrated and there should also be no major problem with the safety of Ramelteon.

4.(iii).A. (5) Long-term treatment study (5.3.5.2-1.1, OCT002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single-blind study was conducted to evaluate the efficacy and safety of long-term treatment with Ramelteon in patients who completed the treatment period of a phase II/III study (5.3.5.1-2.1, CCT002) within 4 weeks or more than 3 months ago, and patients with chronic insomnia[20] who had not previously participated in the phase II/III study (5.3.5.1-2.1, CCT002) (Target sample size of 170).

[20] Patients who completed the treatment period of the phase II/III study (5.3.5.1-2.1, CCT002) more than 3 months ago and patients who had not previously participated in the phase II/III study (5.3.5.1-2.1, CCT002) had to be diagnosed with primary insomnia (DSM-IV) and meet the following criteria.

First screening phase (at the start of the lead-in period):

1) Daytime complaints associated with disturbed sleep for at least 3 months
2) Subjective sleep latency ≥60 minutes and total sleep time <6.5 hours

Second screening phase (at the end of the lead-in period):

Subjective sleep latency ≥45 minutes on at least 3 nights of the lead-in period

During the lead-in period, placebo was to be orally administered once daily 30 minutes prior to bedtime for 7 days. During the treatment period, Ramelteon was to be started at a dose of 4 or 8 mg and after at least 4 weeks of treatment, the dose was allowed to be increased up to 16 mg[21] if the effect was insufficient[22] (The dose was allowed to be reduced to 4 mg if not tolerated. If the 4 mg dose was not tolerated, treatment was to be discontinued.). Ramelteon was to be orally administered once daily 30 minutes prior to bedtime and the duration of treatment was 24 weeks.

Among a total of 191 treated subjects, 190 subjects (the starting dose, 4 mg in 95 subjects and 8 mg in 95 subjects) were included in the FAS and analyzed for efficacy and safety. Excluded was 1 subject who was found to have participated in another clinical study (5.3.5.1-2.1, CCT002).

The daily dose of Ramelteon at final assessment (mean ± SD) was 7.92 ± 3.95 mg and the distribution of the doses at final assessment was as follows: 4 mg (33.7% [64 of 190 subjects]), 8 mg (50.5% [96 of 190 subjects]), and 16 mg (15.8% [30 of 190 subjects]).

The efficacy endpoint of subjective sleep latency (sSL) over time was as shown in the following table.

Table. sSL at different timepoints (minutes)

Timepoint	Lead-in period	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Run-out period
N	190	189	184	183	172	164	160	158	158
sSL	72.86 ± 50.41	58.42 ± 38.47	51.13 ± 33.49	47.88 ± 31.29	42.54 ± 30.12	40.43 ± 29.15	38.69 ± 29.95	38.70 ± 29.12	40.47 ± 29.90

Mean ± SD

The incidence of adverse events (including laboratory test abnormalities) was 77.4% (147 of 190 subjects). No deaths were reported. Other serious adverse events were reported by 2 subjects (pyelonephritis and synovitis, one case each), but a causal relationship to study drug was denied for both events.

The incidence of adverse events for which a causal relationship to study drug could not be denied was 11.6% (22 of 190 subjects) and the main adverse events were γ-GTP increased (4 subjects), hepatic function abnormal (3 subjects), somnolence (3 subjects), ALT (GPT) increased (2 subjects), etc.

There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse rate) or ECG.

Based on the above, the applicant explained that there should be no major problem with the efficacy and safety of 24-week treatment with Ramelteon at doses up to 16 mg.

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[21] If the effect of the 4 mg dose was insufficient, the dose was to be increased to 8 mg and if the effect of the 8 mg dose was insufficient, the dose was to be increased to 16 mg.

[22] If no improvement was found as assessed by PGI (Patient Global Impression of Therapy).

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

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

4.(iii).B.(1).1) Phase III study design (5.3.5.1-3.1, CCT003)

(a) Justification for the screening criteria regarding subjective sleep latency during the lead-in period

PMDA asked the applicant to provide a justification for the screening criteria for a phase III study (5.3.5.1-3.1, CCT003), i.e. explain the reason for specifying the following criterion in addition to the screening criteria for a phase II/III study (5.3.5.1-2.1, CCT002): "the difference of the average subjective sleep latency from the first 3 days to the last 3 days of the lead-in period was within ± 30 minutes."

The applicant explained as follows:

In the phase II/III study (5.3.5.1-2.1, CCT002), subjective sleep latency (sSL) over the first week of double-blind treatment (minutes, least square mean ± SE) was 64.50 ± 1.29 in the placebo group, 64.65 ± 1.31 in the Ramelteon 4 mg group, and 61.40 ± 1.29 in the Ramelteon 8 mg group and there was no statistically significant difference in sSL between either 4 mg or 8 mg of Ramelteon and placebo (4 mg group, P = 0.9315; 8 mg group, P = 0.0905; ANCOVA with baseline as a covariate and treatment as a factor). On the other hand, the results of subgroup analyses by patient background factors (age, gender, Body Mass Index [BMI], smoking status, habitual alcohol use, habitual caffeine use, prior therapy with hypnotics, the duration of disease, the difference of sSL during the lead-in period) were as shown in the following table and the effect size of 8 mg of Ramelteon vs. placebo tended to be greater in the subgroups of "non-smokers or previous smokers," "habitual alcohol use," "no habitual caffeine use," "no prior therapy with hypnotics," "a duration of disease < 1 year," and "a small or positive difference of sSL during the lead-in period." As for smoking status, habitual alcohol use, habitual caffeine use, prior therapy, and the duration of disease, Ramelteon is potentially administered to patients with these background factors after the market launch and it was considered necessary to investigate the efficacy and safety of Ramelteon in these patients. Thus, the criteria regarding these background factors were not specified for the phase III study (5.3.5.1-3.1, CCT003). sSL is a subjective measure and is affected by various factors, which may make drug evaluation difficult. However, it was considered that patients with a small or positive difference of sSL during the lead-in period were unlikely to experience a placebo effect and were able to self-assess sSL accurately to a certain extent, allowing for appropriate drug evaluation.

Table. An investigation of factors potentially affecting sSL at Week 1 in phase II/III study (5.3.5.1-2.1, CCT002)

		N		Analysis to adjust individually[a)]		Analysis to adjust simultaneously[b)]	
		Placebo	Ramelteon 8 mg	Point estimate	*P*-value	Point estimate	*P*-value
Overall population		380	378	-3.10	0.091	-7.30	0.045
Age	≥ 65 years	91	82	-3.05	0.427	-7.91	0.111
	< 65 years	289	296	-3.15	0.131	-6.68	0.071
Gender	Female	240	237	-2.25	0.329	-6.27	0.122
	Male	140	141	-4.51	0.133	-8.33	0.056
BMI	≥ 23	160	165	-3.03	0.278	-6.28	0.130
	≥ 20 and < 23	121	123	-2.64	0.415	-6.73	0.126
	< 20	99	90	-3.67	0.318	-8.89	0.078
Smoking status	Non-smoker	215	177	-4.24	0.096	-8.89	0.036
	Previous smoker	56	65	-6.34	0.166	-9.13	0.085
	Current smoker	109	136	-0.37	0.909	-3.88	0.401
Alcohol	No	307	313	-2.75	0.175	-5.69	0.113
	Yes	73	65	-4.98	0.246	-8.90	0.079
Caffeine	No	81	83	-5.08	0.195	-8.45	0.083
	Yes	299	295	-2.59	0.210	-6.15	0.086
Prior therapy	None	231	230	-5.37	0.022	-9.99	0.009
	Non-BZD	39	31	-2.29	0.705	-8.72	0.188
	BZD	110	117	1.76	0.599	-3.18	0.464
Duration of disease	< 1 year	89	102	-7.91	0.030	-10.41	0.031
	≥ 1 year	291	276	-1.53	0.468	-4.19	0.244
Difference of sSL during the lead-in period	≥ 5 minutes	99	114	-5.87	0.089	-10.38	0.028
	-15 to 5 minutes	124	120	-4.12	0.200	-7.59	0.095
	< -15 minutes	157	144	-0.43	0.883	-3.92	0.353

a) ANCOVA with baseline, individual background factor, treatment, and individual background factor-by-treatment interaction as factors
b) ANCOVA with baseline, all background factors, treatment, and all background factor-by-treatment interactions as factors

Based on the above, the applicant calculated the percentage of relevant subjects from the phase II/III study (5.3.5.1-2.1, CCT002). As a result, 40% of the overall population had a ≥15-minute reduction in sSL and 20% of the overall population had a ≥30-minute reduction in sSL during the lead-in period. The results of a subgroup analysis according to the difference of sSL during the lead-in period (<30 minutes or ≥30 minutes) were as shown in the following table and the efficacy of Ramelteon was suggested in patients with a difference of sSL during the lead-in period of ≥-30 minutes and <+30 minutes. Therefore, from a feasibility standpoint, it was decided to enroll patients into the phase III study (5.3.5.1-3.1, CCT003) if the difference of sSL during the lead-in period was within ± 30 minutes.

Table. Influences of difference of sSL during the lead-in period in phase II/III study (5.3.5.1-2.1, CCT002)

Difference of sSL during the lead-in period	Timepoint	Placebo	Ramelteon 8 mg	Difference from placebo [95% CI]	*P*-value
≥ -30 minutes and < +30 minutes	Lead-in period	69.53 ± 1.94 (267)	65.10 ± 1.97 (258)	-	-
	Week 1	60.53 ± 1.26 (267)	54.85 ± 1.29 (258)	-5.68 [-9.23, -2.14]	0.0017
	Week 2	54.48 ± 1.26 (265)	50.30 ± 1.30 (252)	-4.17 [-7.72, -0.62]	0.0213
< -30 minutes or ≥ +30 minutes	Lead-in period	104.28 ± 5.31 (113)	104.03 ± 5.15 (120)	-	-
	Week 1	73.59 ± 3.10 (113)	77.11 ± 3.01 (120)	3.52 [-5.00, 12.01]	0.4158
	Week 2	65.95 ± 3.29 (113)	74.40 ± 2.25 (116)	8.46 [-0.64, 17.55]	0.068

Least square mean ± SE (N)
ANCOVA with baseline as a covariate and treatment as a factor

(b) Selection and timing of primary endpoint

PMDA asked the applicant to explain the reason for selecting sSL as the primary endpoint for a phase III study (5.3.5.1-3.1, CCT003) and the appropriateness of the timing of the primary endpoint (Week 1).

The applicant explained as follows:

As Ramelteon should contribute to sleep induction based on its mechanism of action [see "3.(i) Summary of pharmacology studies"], primarily, reductions in sleep latency were measured. There are objective and

subjective means of measuring sleep latency, i.e. objective measurements of LPS by PSG and subjective measurements of sSL by sleep questionnaire. Although LPS by PSG is considered more sensitive than sSL, PSG is troublesome and difficult to be employed in a large study. The US guideline for clinical evaluation of hypnotics (Prien RF and Robinson DS eds, *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines; In association with the NIMH and the ACNP*, Raven Press, 1994;579-592) recommends the use of a sensitive PSG parameter for a dose-response study and the use of a subjective parameter, which can be measured in a large number of patients, for a confirmatory study. Thus, also in Japan, LPS by PSG for a dose-response study (5.3.5.1-1, CCT001) or sSL by sleep questionnaire for a phase II/III study (5.3.5.1-2.1, CCT002) and the phase III study (5.3.5.1-3.1, CCT003) was selected as the primary endpoint.

Since the Japanese guideline for clinical evaluation of hypnotics ("Guideline for Clinical Evaluation of Hypnotics" [Notification No. 18 of the Director, Evaluation Division I, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated July 18, 1988]) recommends a duration of treatment of at least 2 weeks and the US guideline for clinical evaluation of hypnotics (Prien RF and Robinson DS eds, *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines; In association with the NIMH and the ACNP*, Raven Press, 1994;579-592) recommends 1 to 2 weeks for short-term evaluation, the phase III study (5.3.5.1-3.1, CCT003) had an evaluation period of 2 weeks. However, rapid onset of action is clinically important for a reduction in sleep latency and in the phase II/III study (5.3.5.1-2.1, CCT002), the results of a subgroup analysis including patients meeting the screening criteria for the phase III study (5.3.5.1-3.1, CCT003) (the difference of sSL during the lead-in period was within ± 30 minutes) were as shown in the following table and a statistically significant difference from placebo in sSL was observed at Week 1. Thus, Week 1 was chosen as the timing of the primary endpoint.

Table. sSL in patients with a difference of sSL during the lead-in period of ≥ -30 minutes and < +30 minutes in phase II/III study (5.3.5.1-2.1, CCT002)

	Placebo	Ramelteon 4 mg	Ramelteon 8 mg	Difference from placebo [95% CI] *P*-value[a)]	
				Ramelteon 4 mg	Ramelteon 8 mg
Lead-in period	69.53 ± 1.94 (267)	73.79 ± 1.95 (265)	65.10 ± 1.97 (258)	-	-
Week 1	60.53 ± 1.26 (267)	58.00 ± 1.27 (265)	54.85 ± 1.29 (258)	-2.53 [-6.05, 0.99] 0.1592	-5.68 [-9.23, -2.14] 0.0017
Week 2	54.48 ± 1.26 (265)	51.20 ± 1.27 (261)	50.30 ± 1.30 (252)	-3.28 [-6.79, 0.24] 0.0674	-4.17 [-7.72, -0.62] 0.0213

Least square mean ± SE (N)
a) ANCOVA with baseline as a covariate and treatment as a factor

(c) Dose selection

PMDA asked the applicant to explain why only an 8 mg dose of Ramelteon was used in a phase III study (5.3.5.1-3.1, CCT003).

The applicant explained as follows:

Because a phase II study using LPS by PSG as a measure of efficacy (5.3.5.1-1, CCT001) suggested the efficacy of Ramelteon at doses ≥8 mg, a phase II/III study (5.3.5.1-2.1, CCT002) was designed to allow comparison among three treatment groups (placebo, 4 mg and 8 mg of Ramelteon) at Week 1, followed by administration of Ramelteon at escalated doses up to 16 mg in Week 3 onward, with a view to the usage in clinical practice. However, efficacy was not demonstrated at a dose of 4 mg for sSL at Week 1 and the

changes in sSL from Week 2 to Week 3 were as shown in the following table and the change in sSL after a dose increase from 4 mg to 8 mg (group M) or from 8 mg to 16 mg (group H) was not greater than the change in sSL after switching from placebo to 4 mg of Ramelteon (group L). Therefore, it was considered that a dose increase from 8 mg to 16 mg would not provide sufficient effect. Based on the above, the optimal dose of Ramelteon was determined to be 8 mg and an 8 mg dose of Ramelteon was chosen for the phase III study (5.3.5.1-3.1, CCT003).

Table. sSL at Weeks 2 and 3 (FAS) in phase II/III study (5.3.5.1-2.1, CCT002)

		Group L	Group M	Group H
Week 2 (before dose increase)	Treatment	Placebo	4 mg	8 mg
	N	378	364	368
	sSL (minutes)[a)]	57.9 ± 1.33	57.9 ± 1.35	57.5 ± 1.35
Week 3 (after dose increase)	Treatment	4 mg	8 mg	16 mg
	N	370	361	362
	sSL (minutes)[a)]	51.5 ± 1.39	53.9 ± 1.41	52.4 ± 1.40
Week 3 − Week 2	sSL (minutes)	-5.99 ± 1.22	-3.79 ± 1.23	-4.79 ± 1.23

Least square mean ± SE
ANCOVA with baseline as a covariate and treatment as a factor
a) sSL at Week 2 was defined as the mean of values from Day 8 to Day 14 and sSL at Week 3 was defined as the mean of values from Day 15 to Day 21.

PMDA considers that there is no major problem with the phase III study design (5.3.5.1-3.1, CCT003) formulated in consideration of the above (a) to (c) [for the interpretation of the obtained results, see "4.(iii).B.(1).2) Efficacy of Ramelteon in reducing sleep latency"].

4.(iii).B.(1).2) Efficacy of Ramelteon in reducing sleep latency

(a) Clinical significance of sSL and LPS improvement and the optimal dose of Ramelteon

PMDA asked the applicant to explain the relationship between subjective sleep latency (sSL) and latency to persistent sleep (LPS) in efficacy evaluation of Ramelteon and the clinical significance of Ramelteon, taking account of the difference in sSL between Ramelteon and placebo (effect size) in a phase III study (5.3.5.1-3.1, CCT003).

The applicant explained as follows:

Since $GABA_A$ receptor agonists, i.e. currently marketed hypnotics (BZD and non-BZD), have anxiolytic and muscle-relaxing effects etc. in addition to a sleep-promoting effect via activation of the sleep center, their effect size for a subjective measure of sSL tends to be larger than that for LPS. In melatonin receptor agonists such as Ramelteon, such effects are less frequent and only have a sleep-promoting effect. Therefore, their effect size for sSL tends to be equal to or smaller than that for LPS. According to Buscemi et al.'s report (Buscemi N et al, *General Internal Medicine*, 2007;22: 1335-1350), a meta-analysis of RCTs revealed that the effect sizes for LPS and sSL with their 95% CIs (minutes) were -10.02 [-16.60, -3.44] and -19.56 [-23.87, -15.25], respectively, for BZD and -12.83 [-16.87, -8.80] and -17.00 [-20.01, -13.99], respectively, for non-BZD. The results of comparison of the effect sizes for sSL and LPS in a sleep laboratory in a zopiclone-controlled foreign clinical study (5.3.5.4-7, EC301) were as shown in the following table. While the effect size of Ramelteon for sSL was not larger than that for LPS, the effect size of the $GABA_A$ receptor agonist for sSL tended to be larger than that for LPS. Therefore, it is considered difficult to compare the effect size between drugs with different mechanisms of action.

Table. Effect sizes of Ramelteon and zopiclone for LPS and sSL (minutes) (5.3.5.4-7, EC301)

Treatment group	Timepoint	LPS	sSL
Ramelteon	Nights 1-2	-9.71 [-18.51, -0.90]	-8.29 [-17.56, 0.98]
	Nights 27-28	-1.94 [-10.54, 6.66]	4.10 [-6.94, 15.13]
Zopiclone	Nights 1-2	-6.10 [-14.84, 2.65]	-17.78 [-26.94, -8.62]
	Nights 27-28	5.93 [-2.62, 14.47]	-8.08 [-18.98, 2.83]

[95% CI]

The effect size of zolpidem for LPS has been reported to be -28 to 1.1 minutes (Roth T et al, *Sleep*, 1995;18: 246-251, Walsh JK et al, *J Clin Psychopharmacol*, 1990;10: 184-189, Scharf MB et al, *J Clin Psychiatry*, 1991;52: 77-83) and the effect size of eszopiclone for LPS has been reported to be -19.5 to -6.2 minutes (Lunesta: *Summary Basis of Approval [NDA21-476]*) and the effect size of 8 mg of Ramelteon for LPS was -13.15 minutes in a Japanese phase II study (5.3.5.1-1, CCT001) and -13.5 to -15.3 minutes in foreign clinical studies (Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-9, TL021; 5.3.5.1-4, EC302). Thus, the effect size of 8 mg of Ramelteon is considered similar to that of currently marketed drugs. Although the effect size of sSL reductions for Ramelteonis smaller compared to sSL reductions with $GABA_A$ receptor agonists reported so far, the phase III study (5.3.5.1-3.1, CCT003) has demonstrated the superiority of 8 mg of Ramelteon to placebo, Ramelteon has been shown to reduce LPS to a similar degree as currently marketed hypnotics, and sSL reductions with $GABA_A$ receptor agonists are contributed to by its anxiolytic and muscle-relaxing effects etc., which may induce rebound insomnia, dependence, fall, staggering, withdrawal symptoms, etc. Taking account of these findings, the difference in sSL between Ramelteon and placebo observed in the phase III study (5.3.5.1-3.1, CCT003) is considered of clinical significance.

PMDA considers as follows:

Whether the between-treatment difference observed in the phase III study (5.3.5.1-3.1, CCT003) is of adequate clinical significance or not is not defined. However, since the phase II study (5.3.5.1-1, CCT001) showed that Ramelteon reduced LPS to a similar degree as currently marketed hypnotics and the phase III study using sSL as the primary endpoint (5.3.5.1-3.1, CCT003) demonstrated the superiority of Ramelteon to placebo, it is acceptable to conclude, based on these study results, that the efficacy of 8 mg of Ramelteon has been demonstrated. In addition, there has been no major problem with its safety. Thus, there is no major problem with choosing 8 mg as the recommended clinical dose for Ramelteon. The pharmacological mechanism of action of Ramelteon is different from those of currently marketed hypnotics and the applicant claimed that anxiolytic and muscle-relaxing effects etc. contribute to sSL reductions and this possibility can not be ruled out. Therefore, it is necessary to continue to determine how much improvement in sSL is clinically significant for a hypnotic without anxiolytic and muscle-relaxing effects.

(b) Efficacy of long-term use of Ramelteon

PMDA asked the applicant to explain why there was a statistically significant difference in sSL at Week 1 between 8 mg of Ramelteon and placebo, but the between-treatment difference in sSL was smaller and did not reach statistical significance at Week 2 in a phase III study (5.3.5.1-3.1, CCT003).

The applicant explained as follows:

In the phase III study (5.3.5.1-3.1, CCT003), the difference in sSL between the placebo and Ramelteon groups (-4.54 minutes) observed at Week 1 was reduced to -2.36 minutes at Week 2. Meanwhile, in foreign clinical studies (Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-12, TL069), there was no particular trend towards a reduction in the difference from placebo from Week 1 to Week 2 onward, as shown in the following table.

Table. sSL over time in Japanese and foreign clinical studies (minutes) (FAS)

		Timepoint	Placebo	Ramelteon 8 mg	Difference from placebo [95% CI]	*P*-value[a,b)]
Japan	CCT003	Baseline	77.42 ±1.39 (482)	77.13 ±1.38 (489)	-	-
		Week 1	65.69 ± 0.97 (481)	61.15 ± 0.97 (489)	-4.54 [-7.23, -1.85]	0.0010
		Week 2	59.47 ± 1.04 (478)	57.11 ± 1.04 (478)	-2.36 [-5.25, 0.53]	0.1093
Overseas	TL021	Baseline	74.7 ± 3.66 (131)	71.4 ± 3.58 (139)	-	-
		Week 1	64.3 ± 2.38 (131)	62.9 ± 2.34 (138)	-1.4 [-7.8, 5.0]	0.665
		Week 3	61.8 ± 2.36 (131)	56.6 ± 2.32 (138)	-5.2 [-11.6, 1.1]	0.104
	TL020	Baseline	85.5 ± 2.99 (287)	85.2 ± 3.03 (277)	-	-
		Week 1	74.4 ± 2.17 (283)	74.8 ± 2.20 (270)	0.4 [-5.5, 6.3]	0.888
		Week 2	71.4 ± 2.10 (284)	69.4 ± 2.14 (270)	-2.1 [-7.8, 3.7]	0.481
		Week 3	70.7 ± 2.14 (284)	69.5 ± 2.18 (270)	-1.3 [-7.1, 4.6]	0.668
	TL069	Baseline	83.8 ± 2.1 (274)	84.8 ± 2.1 (272)	-	-
		Week 1	73.1 ± 1.8 (270)	69.0 ± 1.8 (261)	-4.1 [-8.9, 0.6]	0.088
		Week 2	71.0 ± 1.8 (271)	68.2 ± 1.8 (262)	-2.8 [-7.6, 2.0]	0.258
		Week 3	71.8 ± 1.9 (271)	66.9 ± 1.9 (262)	-4.9 [-10.0, 0.2]	0.060

Least square mean ± SE (N)

a) ANCOVA with baseline as a covariate and treatment as a factor (CCT003, TL020)

b) ANCOVA with baseline as a covariate and treatment and center as factors (TL021, TL069)

The applicant explained why the trend was different between Japan and overseas as follows:

In the foreign clinical studies (Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-12, TL069), the percent change from baseline in sSL in the placebo group was -13.9% to -12.8% at Week 1 and -17.3% to -14.3% at Week 2 or 3 and it seemed that a steady state was nearly achieved at Week 1. On the other hand, in the phase III study (5.3.5.1-3.1, CCT003), the percent change from baseline in the placebo group was -15.2% at Week 1 and -23.2% at Week 2 and the placebo group had a reduction in sSL also at Week 2. Therefore, the Japanese phase III study (5.3.5.1-3.1, CCT003) failed to demonstrate a statistically significant difference in sSL at Week 2 between the Ramelteon and placebo groups, due to a different placebo effect between Japan and overseas.

Then, in order to investigate the cause for a different placebo effect between the studies in Japan and overseas, the demographic/baseline characteristics of patients (gender, age, BMI, smoking habit, habitual alcohol use, habitual caffeine use, the duration of disease, prior therapy with BZD, baseline sSL) were compared between the Japanese phase III study (5.3.5.1-3.1, CCT003) and the foreign clinical studies (Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-12, TL069). As a result, BMI was slightly higher and the proportion of patients with habitual alcohol use and the proportion of patients with smoking habit were higher among the patients enrolled into the foreign clinical studies. Changes in sSL in the placebo groups in the Japanese and foreign clinical studies were analyzed, adjusting for these factors individually and simultaneously, but there was no consistent trend in sSL changes. Thus, the cause for a greater sSL change in the placebo group at Week 2 in the phase III study (5.3.5.1-3.1, CCT003) compared with the foreign clinical studies (Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-12, TL069) was not defined.

PMDA asked the applicant to explain the clinical significance of administering Ramelteon for ≥1 week and the duration of the efficacy of Ramelteon.

The applicant explained as follows:

Using the patient background factors (age, gender, BMI, smoking, alcohol use, caffeine use, the duration of disease, the difference of sSL during the lead-in period, Zung Self-Rating Depression Scale [SDS],[23] compliance[24]) in the phase III study (5.3.5.1-3.1, CCT003), factors potentially affecting the effect sizes for sSL at Weeks 1 and 2 (the difference between Ramelteon and placebo) were investigated as shown in the following table. The effect size at Week 1 was close to the effect size at Week 2 in the subgroups of "current smokers," "the difference of sSL during the lead-in period of -30 to 0 minutes," and "good compliance" while the effect size at Week 2 was smaller than that at Week 1 in other subgroups. Thus, these factors may affect sSL.

Table. Effect size for sSL in subgroups of phase III study (5.3.5.1-3.1, CCT003)

		Week 1				Week 2			
		N		Analysis to adjust individually[a]	Analysis to adjust simultaneously[b]	N		Analysis to adjust individually[a]	Analysis to adjust simultaneously[b]
		Placebo	Ramelteon	Point estimate (*P*-value)	Point estimate (*P*-value)	Placebo	Ramelteon	Point estimate (*P*-value)	Point estimate (*P*-value)
Overall population		481	489	-4.54 (0.001)	-2.82 (0.547)	478	478	-2.36 (0.109)	-0.27 (0.956)
Age	≥ 65 years	27	30	-0.28 (0.961)	-1.06 (0.878)	27	29	0.49 (0.935)	0.40 (0.957)
	< 65 years	454	459	-4.79 (0.001)	-4.59 (0.230)	451	449	-2.52 (0.097)	-0.94 (0.817)
Gender	Female	304	307	-5.81 (0.001)	-3.72 (0.450)	302	300	-2.62 (0.159)	0.63 (0.905)
	Male	177	182	-2.36 (0.295)	-1.92 (0.697)	176	178	-1.94 (0.422)	-1.17 (0.823)
BMI	≥ 23	158	156	-0.90 (0.709)	0.60 (0.904)	156	152	0.88 (0.735)	3.47 (0.514)
	≥ 20 and < 23	177	192	-6.23 (0.005)	-4.51 (0.364)	176	189	-4.55 (0.057)	-2.72 (0.607)
	< 20	146	141	-6.28 (0.013)	-4.55 (0.394)	146	137	-3.02 (0.265)	-1.57 (0.783)
Smoking status	Non-smoker[c]	450	453	-4.11 (0.004)	0.99 (0.801)	447	443	-1.87 (0.221)	4.06 (0.331)
	Smoker	31	36	-10.97 (0.036)	-6.63 (0.315)	31	35	-9.88 (0.078)	-4.61 (0.513)
Alcohol	No	446	460	-4.89 (0.001)	-4.93 (0.237)	443	449	-2.91 (0.057)	-4.35 (0.328)
	Yes	35	29	0.41 (0.939)	-0.72 (0.913)	35	29	5.13 (0.370)	3.80 (0.583)
Caffeine	No	164	180	-2.39 (0.301)	-1.03 (0.840)	162	177	-1.54 (0.534)	0.91 (0.867)
	Yes	317	309	-5.69 (0.001)	-4.61 (0.325)	316	301	-2.83 (0.123)	-1.46 (0.770)
Duration of disease	< 1 year	231	240	-2.14 (0.278)	-1.10 (0.828)	229	230	0.60 (0.776)	2.16 (0.686)
	≥ 1 year	250	249	-6.77 (<0.001)	-4.55 (0.338)	249	248	-5.09 (0.013)	-2.71 (0.592)
Difference of sSL during the lead-in period	0-30 minutes	214	217	-6.72 (0.001)	-5.10 (0.308)	213	214	-1.92 (0.382)	-0.39 (0.942)
	-30 to 0 minutes	267	272	-2.79 (0.129)	-0.54 (0.910)	265	264	-2.73 (0.168)	-0.16 (0.976)
SDS	≤ 38	237	233	-7.28 (< 0.001)	-6.91 (0.149)	235	229	-5.07 (0.016)	-4.39 (0.390)
	39-47	189	188	-2.40 (0.274)	-1.35 (0.784)	188	183	-0.91 (0.699)	0.23 (0.964)
	≥ 48	55	68	-1.06 (0.784)	-0.21 (0.971)	55	66	3.18 (0.443)	3.34 (0.596)
Compliance	Good	245	260	-4.75 (0.013)	-2.80 (0.563)	245	260	-4.35 (0.032)	-2.23 (0.665)
	Poor	236	229	-4.32 (0.030)	-2.85 (0.564)	233	218	0.03 (0.989)	1.69 (0.749)

a) ANCOVA with baseline, individual background factor, treatment, and individual background factor-by-treatment interaction as factors
b) ANCOVA with baseline, all background factors, treatment, and all background factor-by-treatment interactions as factors
c) Including previous smokers

In the phase III study (5.3.5.1-3.1, CCT003), sSL over time in patients with good compliance[24] was as shown in the following table, and there was a statistically significant difference between the Ramelteon and placebo groups also at Week 2 and the efficacy of 8 mg of Ramelteon persisted. Although smoking status and the difference of sSL during the lead-in period were also identified as potentially affecting the efficacy

23) A 20-item measure of the symptoms of depression (20-80 scores). Higher scores indicate higher levels of depression.

24) Good compliance was defined as patients who took study drug throughout the double-blind period and completed a sleep questionnaire within 60 minutes of getting out of bed. Poor compliance was defined as patients other than those with "good compliance."

of Ramelteon at Week 2, rigorous evaluation was difficult due to a limited number of smokers in the phase III study (5.3.5.1-3.1, CCT003) and the persistence of efficacy only in smokers was not observed in the phase II/III study (5.3.5.1-2.1, CCT002). Also, the results of a subgroup analysis by median difference of sSL during the lead-in period (≥-5 minutes or <-5 minutes) in the phase III study (5.3.5.1-3.1, CCT003) revealed no major difference in the persistence of efficacy between the subgroups. Therefore, it is considered that these factors have little effect on efficacy.

Table. sSL in patients with good compliance (minutes) in phase III study (5.3.5.1-3.1, CCT003)

	Placebo	Ramelteon	Between-treatment difference[a)] [95% CI]	*P*-value[b)]
Lead-in period	76.37 ± 1.92 (245)	76.76 ± 1.87 (260)	-	-
Week 1	65.35 ± 1.35 (245)	60.58 ± 1.31 (260)	-4.77 [-8.46, -1.08]	0.0114
Week 2	58.96 ± 1.42 (245)	54.60 ± 1.38 (260)	-4.36 [-8.24, -0.47]	0.0279
Run-out period	55.95 ± 1.34 (245)	53.69 ± 1.30 (258)	-2.26 [-5.92, 1.41]	0.2276

Least square mean ± SE (N)
a) sSL in Ramelteon group − sSL in placebo group
b) ANCOVA with baseline as a covariate and treatment as a factor

Based on the above, the applicant explained as follows:
"Patients with good compliance" are considered to be highly aware of insomnia treatment and clinical trials. In everyday medical practice, if healthcare professionals such as physicians give a guidance to encourage patients to take control of their lifestyle and patients comply with the guidance, the efficacy of Ramelteon can be maintained. Therefore, there is no need to limit the duration of treatment with Ramelteon as long as the "Important Precautions" section of the package insert will advise physicians to give lifestyle guidance to patients and periodically review the need for continued treatment.

The applicant also explained about the efficacy of long-term treatment with Ramelteon as follows:
sSL over time in patients treated with 8 mg of Ramelteon only in a Japanese long-term treatment study (5.3.5.2-1.1, OCT002) and LPS and sSL over time in patients treated with 8 mg of Ramelteon or placebo for 6 months in a foreign clinical study (5.3.5.1-4, EC302) were as shown in the following table and it seemed that the efficacy of Ramelteon persisted up to 6 months in both Japanese and foreign clinical studies.

Table. LPS and sSL over time (minutes) (Japan, 5.3.5.2-1.1, OCT002; Overseas, 5.3.5.1-4, EC302, OC)

	Japan	Overseas					
		sSL			LPS		
	Ramelteon	Placebo	Ramelteon	*P*-value[a)]	Placebo	Ramelteon	*P*-value[a)]
Lead-in period	70.51 ± 47.58 (74)	78.53 ± 43.01 (223)	79.76 ± 40.83 (224)	-	69.53 ± 42.52 (222)	70.75 ± 41.44 (225)	-
Week 1	54.35 ± 37.32 (74)	64.19 ± 41.30 (220)	51.74 ± 34.49 (221)	< 0.001	46.47 ± 36.88 (222)	32.25 ± 29.52 (224)	< 0.001
Week 4 (1 month)	43.04 ± 27.64 (70)	57.47 ± 39.63 (208)	48.60 ± 35.15 (210)	0.006	38.32 ± 34.45 (208)	30.71 ± 30.07 (212)	0.008
Week 12 (3 months)	37.42 ± 27.34 (66)	54.81 ± 45.09 (190)	48.96 ± 42.03 (191)	0.165	36.26 ±30.51 (193)	31.15 ± 33.56 (195)	0.097
Week 20 (5 months)	33.81 ± 24.30 (61)	53.24 ± 38.31 (185)	43.58 ± 33.98 (172)	0.010	39.06 ± 39.83 (186)	30.63 ± 32.01 (175)	0.022
Week 24 (6 months)	38.83 ± 29.11 (60)	51.88 ± 39.56 (179)	44.73 ± 37.76 (164)	0.073	38.96 ± 41.05 (182)	28.44 ± 25.65 (168)	0.003

Mean ± SD (N)
a) ANCOVA with baseline as a covariate and treatment as a factor

PMDA considers as follows:

In the Japanese phase III study (5.3.5.1-3.1, CCT003), although there was a statistically significant difference in the primary endpoint of sSL at Week 1 between the Ramelteon and placebo groups, the between-treatment difference in the secondary endpoint of sSL at Week 2 was small and did not reach statistical significance. This means that the persistence of the effectiveness of Ramelteon in Japanese patients has not been defined. On the other hand, the foreign placebo-controlled study (5.3.5.1-4, EC302) demonstrated the persistence of the effectiveness of Ramelteon up to 6 months, and the Japanese phase III study (5.3.5.1-3.1, CCT003) suggested the efficacy of Ramelteon also at Week 2 in "patients with good compliance." As the Japanese long-term treatment study (5.3.5.2-1.1, OCT002) was an open-label study, its results need to be interpreted carefully, but they do not contradict the persistence of the effectiveness of Ramelteon. From a safety point of view, there have so far been no adverse events of concern etc. following long-term treatment with Ramelteon [see "4.(iii).B.(3) Safety of Ramelteon"]. Taking account of these findings, although administration of Ramelteon without careful consideration should be avoided, physicians may choose to continue treatment with Ramelteon while giving appropriate guidance in patients who have responded to Ramelteon, after balancing the benefits and risks. Therefore, the package insert should state that after the initiation of Ramelteon treatment, its efficacy and safety should be monitored continuously, administration without careful consideration should be avoided, and patients should also be instructed to improve their lifestyle. If such statements are included in the package insert, it will not be necessary to limit the duration of treatment with Ramelteon. Specific statements etc. will be determined, taking account of comments from the Expert Discussion [see4.(iii).B.(5) Positioning of Ramelteon in the treatment of insomnia and proper use].

4.(iii).B.(1).3) Effects of Ramelteon on sleep parameters other than sleep latency

PMDA asked the applicant to explain the effects of Ramelteon on sleep parameters.

The applicant explained as follows:

In a phase III study (5.3.5.1-3.1, CCT003), the total sleep time and the number of awakenings as assessed by the sleep questionnaire were as shown in the following table. The total sleep time at Week 1 was statistically significantly prolonged in the Ramelteon group compared to the placebo group, but there was no statistically significant difference at Week 2. For the number of awakenings, there was no statistically significant difference at Week 1, but a statistically significant reduction was observed in the Ramelteon group compared to the placebo group at Week 2.

Table. Effects of Ramelteon on total sleep time and the number of awakenings (5.3.5.1-3.1, CCT003)

		Placebo	Ramelteon	Between-treatment difference[a)] [95% CI]	*P*-value[b)]
Total sleep time (hours)	Lead-in period	5.24 ± 0.04 (482)	5.29 ± 0.04 (489)	-	-
	Week 1	5.56 ± 0.02 (481)	5.63 ± 0.02 (489)	0.07 [0.00, 0.13]	0.0484
	Week 2	5.69 ± 0.03 (478)	5.74 ± 0.03 (478)	0.04 [-0.03, 0.12]	0.2378
	Run-out period	5.78 ± 0.03 (471)	5.82 ± 0.03 (475)	0.04 [-0.05, 0.12]	0.3832
No. of awakenings	Lead-in period	1.31 ± 0.04 (482)	1.34 ± 0.04 (489)	-	-
	Week 1	1.13 ± 0.02 (481)	1.09 ± 0.02 (489)	-0.04 [-0.11, 0.03]	0.2592
	Week 2	1.07 ± 0.02 (478)	1.00 ± 0.02 (478)	-0.07 [-0.14, -0.00]	0.0469
	Run-out period	1.02 ±0.02 (471)	0.95 ± 0.02 (475)	-0.07 [-0.14, -0.00]	0.0379

Least square mean ± SE (N)

a) Ramelteon group − Placebo group
b) ANCOVA with baseline as a covariate and treatment as a factor

Sleep parameters as measured by PSG in a phase II study (5.3.5.1-1, CCT001) were as shown in the following table. No dose-response relationship was observed for total sleep time, sleep efficiency, or wake time after sleep onset. Although a statistically significant dose-response relationship was observed for the number of awakenings, there was no statistically significant difference between any dose of Ramelteon and placebo. Furthermore, as for sleep architecture in the phase II study (5.3.5.1-1, CCT001), no dose-response relationship was observed for % time in REM, a statistically significant dose-response relationship was observed for % time in Stage 1, % time in Stage 2, and % time in Stage 3/4,[25)] Percent time in Stage 1 was significantly increased and % time in Stage 3/4 was significantly decreased with 8 mg of Ramelteon compared to placebo, and % time in Stage 1 was increased and % time in Stage 2 or Stage 3/4 was decreased also with other doses of Ramelteon. These changes all corresponded to percent changes from baseline of around 3% and should have a minimal effect on sleep architecture.

Table. Sleep parameters and sleep architecture as measured by PSG (Mean of values on Days 1-2 of each treatment period) (5.3.5.1-1, CCT001, FAS)

	Placebo	4 mg	8 mg	16 mg	32 mg	*P*-value [b)]
N	61	62	61	63	63	
Sleep parameter						
Total sleep time (minutes)	391.58 ± 6.82	403.87 ± 5.46 (0.1063)	405.42 ± 5.55 (0.1085)	403.00 ± 5.14 (0.0790)	400.26 ± 6.22 (0.1678)	0.1138
Sleep efficiency[a)] (%)	81.60 ± 1.42	84.14 ± 1.14 (0.1095)	84.46 ± 1.16 (0.1131)	83.96 ± 1.07 (0.0854)	83.39 ± 1.30 (0.1782)	0.1221
Wake time after sleep onset (minutes)	48.57 ± 4.18	46.43 ± 3.70 (0.9088)	51.61 ± 4.77 (0.8552)	49.42 ± 3.90 (0.9968)	54.41 ± 4.41 (0.3289)	0.0893
No. of awakenings	9.30 ± 0.67	8.89 ± 0.52 (0.7402)	9.17 ± 0.52 (0.9972)	9.68 ± 0.63 (0.7752)	10.15 ± 0.64 (0.2873)	0.0194
Sleep architecture						
Stage 1 (%)	16.62 ± 1.20	18.47 ± 1.24 (0.0003)	18.52 ± 1.36 (0.0199)	19.15 ± 1.33 (< 0.0001)	19.11 ± 1.33 (< 0.0001)	< 0.0001
Stage 2 (%)	57.94 ± 1.09	56.76 ± 1.02 (0.1781)	56.35 ± 1.14 (0.0764)	55.34 ± 1.03 (0.0022)	56.99 ± 1.12 (0.3291)	0.0311
Stage 3/4 (%)	3.66 ± 0.70	2.82 ± 0.57 (0.0434)	2.76 ± 0.50 (0.0129)	3.03 ± 0.53 (0.0625)	2.75 ± 0.49 (0.0040)	0.0080
REM (%)	21.82 ± 0.55	21.99 ± 0.50 (0.9833)	22.41 ± 0.51 (0.5810)	22.50 ± 0.53 (0.4180)	21.15 ± 0.54 (0.2720)	0.3961

Least square mean ± SE, *P*-value in parentheses [ANOVA with pairwise comparisons vs. placebo]
a) Sleep efficiency = (total sleep time/total time in bed)×100
b) ANOVA with contrast coefficients of (2, 1, 0, -1, -2)

Furthermore, sleep parameters over time in a foreign clinical study (5.3.5.1-4, EC302) were as shown in the following table. As for the effect of Ramelteon on sleep architecture, % time in Stage 2 was statistically significantly increased and % time in Stage 3/4 was statistically significantly decreased in the Ramelteon group compared with the placebo group at all timepoints. However, as in the Japanese clinical study, these changes were small and Ramelteon should have a minimal effect on sleep architecture.

[25)] Stage 1 or Stage 2 non-REM (Non-rapid eye movement) sleep is classified as “light non-REM sleep” and Stage 3/4 non-REM sleep is classified as “deep non-REM sleep.”

Table. Sleep parameters and sleep architecture as measured by PSG (5.3.5.1-4, EC302, FAS, OC)

Timepoint	Placebo	Ramelteon	Between-treatment difference [95% CI]	*P*-value[a)]
Total sleep time				
Lead-in period	329.72 ± 3.96 (222)	329.28 ± 3.93 (225)	-	-
Week 1	365.73 ± 3.07 (222)	381.08 ± 3.06 (224)	15.36 [6.83, 23.88]	< 0.001
Month 1	374.55 ± 3.14 (208)	380.09 ± 3.11 (212)	5.54 [-3.14, 14.22]	0.210
Month 3	381.09 ± 3.37 (193)	382.31 ± 3.35 (195)	1.21 [-8.14, 10.56]	0.799
Month 5	381.21 ± 3.66 (186)	381.21 ± 3.77 (175)	-0.00 [-10.34, 10.33]	0.999
Month 6	381.75 ± 3.58 (182)	381.38 ± 3.73 (168)	-0.37 [-10.54, 9.80]	0.943
Stage 1 (%)				
Lead-in period	11.51 ± 0.36 (222)	11.33 ± 0.36 (225)	-	-
Week 1	10.61 ± 0.23 (222)	10.60 ± 0.23 (224)	-0.00 [-0.65, 0.65]	0.992
Month 1	10.51 ± 0.27 (208)	10.10 ± 0.27 (212)	-0.41 [-1.16, 0.34]	0.287
Month 3	10.07 ± 0.27 (193)	10.44 ± 0.27 (195)	0.36 [-0.38, 1.11]	0.335
Month 5	10.14 ± 0.25 (186)	10.31 ± 0.26 (175)	0.17 [-0.55, 0.88]	0.641
Month 6	10.21 ± 0.32 (182)	10.06 ± 0.33 (168)	-0.14 [-1.05, 0.76]	0.756
Stage 2 (%)				
Lead-in period	59.56 ± 0.77 (222)	57.09 ± 0.76 (225)	-	-
Week 1	57.78 ± 0.40 (222)	59.93 ± 0.40 (224)	2.15 [1.04, 3.27]	< 0.001
Month 1	57.05 ± 0.42 (208)	58.85 ± 0.42 (212)	1.80 [0.64, 2.97]	0.002
Month 3	57.17 ± 0.47 (193)	59.09 ± 0.46 (195)	1.92 [0.62, 3.22]	0.004
Month 5	57.81 ± 0.49 (186)	59.89 ± 0.51 (175)	2.08 [0.69, 3.48]	0.004
Month 6	57.62 ± 0.54 (182)	60.15 ± 0.56 (168)	2.53 [1.00, 4.06]	0.001
Stage 3/4 (%)				
Lead-in period	10.37 ± 0.70 (222)	12.89 ± 0.69 (225)	-	-
Week 1	12.72 ± 0.34 (222)	9.76 ± 0.34 (224)	-2.96 [-3.90, -2.02]	< 0.001
Month 1	12.74 ± 0.37 (208)	10.94 ± 0.37 (212)	-1.79 [-2.82 , -0.77]	< 0.001
Month 3	12.39 ± 0.40 (193)	10.62 ± 0.40 (195)	-1.77 [-2.88, -0.67]	0.002
Month 5	11.86 ± 0.40 (186)	9.98 ± 0.41 (175)	-1.88 [-3.01, -0.74]	0.001
Month 6	12.41 ± 0.44 (182)	10.60 ± 0.45 (168)	-1.81 [-3.05, -0.57]	0.004
REM (%)				
Lead-in period	18.56 ± 0.39 (222)	18.69 ± 0.39 (225)	-	-
Week 1	18.92 ± 0.29 (222)	19.69 ± 0.29 (224)	0.76 [-0.04, 1.57]	0.063
Month 1	19.75 ± 0.30 (208)	20.06 ± 0.29 (212)	0.32 [-0.50, 1.14]	0.446
Month 3	20.36 ± 0.33 (193)	19.86 ± 0.33 (195)	-0.50 [-1.42, 0.42]	0.288
Month 5	20.19 ± 0.34 (186)	19.82 ± 0.35 (175)	-0.37 [-1.32, 0.58]	0.444
Month 6	19.78 ± 0.35 (182)	19.18 ± 0.37 (168)	-0.60 [-1.60, 0.40]	0.237

Least square mean ± SE (N)
a) ANCOVA with baseline as a covariate and treatment as a factor

PMDA considers as follows:

The Japanese and foreign clinical studies demonstrated no clear improvement of total sleep time, wake time after sleep onset, or the number of awakenings by Ramelteon. Because light non-REM sleep (Stage 1 or Stage 2) was increased and deep non-REM sleep (Stage 3/4) was decreased in the Japanese and foreign clinical studies, the effect of Ramelteon on sleep architecture needs to be determined carefully, also taking account of its association with safety [see "4.(iii).B.(3).1) Neurological and psychiatric adverse events (somnolence, headache, insomnia exacerbated, depression)"].

4.(iii).B.(1).4) Factors affecting the efficacy of Ramelteon

PMDA asked the applicant to explain factors affecting the efficacy of Ramelteon and then describe the appropriate patient population for Ramelteon.

The applicant explained as follows:

In a phase II/III study (5.3.5.1-2.1, CCT002) and a phase III study (5.3.5.1-3.1, CCT003), factors affecting the change in sSL were investigated [see "4.(iii).B.(1).1). (a) Justification for the screening criteria regarding subjective sleep latency during the lead-in period and 4.(iii).B.(1).2).(b) Efficacy of long-term

use of Ramelteon"]. As a result, the effect size tended to be greater in the subgroup of "a small or positive difference of sSL during the lead-in period" in both studies. "Prior therapy with hypnotics" was assessed only in the phase II/III study (5.3.5.1-2.1, CCT002), and SDS and compliance were assessed only in the phase III study (5.3.5.1-3.1, CCT003). These factors may affect the effect size of Ramelteon.

"Patients with a small difference of sSL during the lead-in period" are considered to be those who were able to self-assess sSL accurately to a certain extent [see "4.(iii).B.(1).1).(a) Justification for the screening criteria regarding subjective sleep latency during the lead-in period"]. The efficacy of Ramelteon was lower in "patients with high SDS scores," which is considered due to the mechanism of action of Ramelteon without anxiolytic and muscle-relaxing effects because these patients are considered to be those who had a high level of depression or anxiety. As for "prior therapy with hypnotics", the phase III study (5.3.5.1-3.1, CCT003) did not enroll a patient previously treated with BZD and enrolled only 12 patients previously treated with non-BZD (5 patients in the placebo group, 7 patients in the Ramelteon group). In the phase II/III study (5.3.5.1-2.1, CCT002), the changes in sSL by presence or absence of prior therapy with hypnotics were as shown in the following table and the efficacy of Ramelteon was not demonstrated in patients previously treated with hypnotics.

Table. sSL over time by presence or absence of prior therapy with hypnotics in phase II/III study (minutes) (5.3.5.1-2.1, CCT002) (FAS)

Prior therapy	Timepoint	Placebo	Ramelteon 8 mg	Difference from placebo [95% CI]	*P*-value [a)]
None	Lead-in period	76.50 ± 2.45 (231)	72.65 ± 2.46 (230)	-	-
	Week 1	62.66 ± 1.53 (231)	57.16 ± 1.54 (230)	-5.50 [-9.77, -1.24]	0.0116
	Week 2	55.95 ± 1.59 (229)	53.53 ± 1.62 (222)	-2.41 [-6.88, 2.05]	0.2887
Non-BZD	Lead-in period	80.77 ± 6.21 (39)	76.58 ± 6.97 (31)	-	-
	Week 1	70.58 ± 4.53 (39)	68.29 ± 5.09 (31)	-2.29 [-15.81, 11.23]	0.6857
	Week 2	57.93 ± 4.06 (39)	66.84 ± 4.56 (31)	8.91 [-3.19, 21.02]	0.1473
BZD	Lead-in period	86.60 ± 5.26 (110)	87.14 ± 5.10 (117)	-	-
	Week 1	65.95 ± 2.62 (110)	67.69 ± 2.54 (117)	1.74 [-5.45, 8.93]	0.6343
	Week 2	61.81 ± 2.75 (110)	62.28 ± 2.69 (115)	0.48 [-7.09, 8.04]	0.9018

Least square mean ± SE (N)
a) ANCOVA with baseline as a covariate and treatment as a factor

PMDA asked the applicant to explain the efficacy of Ramelteon in patients switched from other hypnotics and whether a caution statement in the package insert is needed.

The applicant explained as follows:
While a phase II/III study (5.3.5.1-2.1, CCT002) did not demonstrate the efficacy of Ramelteon in patients previously treated with hypnotics, sSL was reduced over time in a long-term treatment study (5.3.5.2-1.1, OCT002), regardless of the presence or absence of prior therapy with hypnotics. The changes in sSL over time by presence or absence of prior therapy with hypnotics were as shown in the following figure. Long-term treatment was also associated with similar efficacy, which does not disagree with the efficacy of Ramelteon in patients previously treated with hypnotics. No specific caution statement is needed.

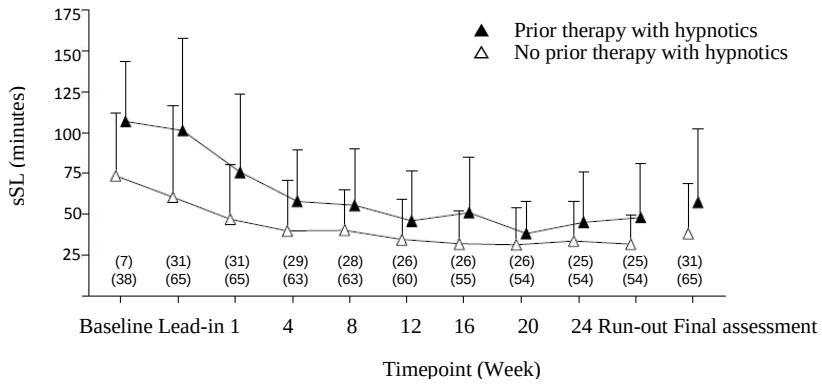

Figure. sSL over time by presence or absence of prior therapy with hypnotics in long-term treatment study (5.3.5.2-1.1, OCT002)

PMDA considers as follows:

The long-term treatment study (5.3.5.2-1.1, OCT002) was an open-label study, and it is difficult to evaluate the efficacy of Ramelteon based only on the results of this study. Taking account of the results of the phase II/III study, which was a placebo-controlled, double-blind, comparative study (5.3.5.1-2.1, CCT002) and a certain placebo effect during the long-term observation in a foreign clinical study (5.3.5.1-4, EC302) etc., the efficacy of Ramelteon in patients previously treated with hypnotics has not been established. Healthcare professionals such as physicians need to correctly understand that Ramelteon possesses no anxiolytic or muscle-relaxing effect, and even has a different pharmacological profile than currently marketed hypnotics. Moreover, it is necessary to consider the possibility that Ramelteon may not provide sufficient effect in patients who have depression or anxiety as the underlying cause of insomnia.

Based on the above, it should be stated in the package insert that the efficacy of Ramelteon in patients previously treated with hypnotics has not been established and that prior to the use of Ramelteon, patients should be closely examined for the underlying cause of insomnia, but the details will be determined, taking account of comments from the Expert Discussion. It is necessary to continue to investigate the efficacy and safety of Ramelteon in patients previously treated with hypnotics via post-marketing surveillance.

4.(iii).B.(2) Impact of Ramelteon on next-day functioning

One of the objectives of insomnia treatment is to improve next-day functioning and the challenge for currently marketed hypnotics is a next-day residual effect. PMDA asked the applicant to explain the impact of Ramelteon on next-day functioning.

The applicant explained as follows:

Of Patient Global Impression (PGI) items in a phase III study (5.3.5.1-3.1, CCT003), “impaired daytime function”[26)] over time was as shown in the following table. There were no statistically significant differences between the Ramelteon and placebo groups, which was possibly due to a lack of sufficient sensitivity. There was a trend towards improvement at Week 2 and the percentage of patients with “worsened” impaired daytime function was low at about less than 3% in both the Ramelteon and placebo groups, and there were no major differences between the two groups. Thus, Ramelteon is unlikely to

[26)] Impaired daytime function associated with insomnia was rated on the following 3-point scale: “improved,” “unchanged,” and “worsened.”

adversely affect daytime function.

Table. Impact of Ramelteon on PGI "impaired daytime function" in phase III study (5.3.5.1-3.1, CCT003) (FAS)

Timepoint	Treatment group	N	Improved	Unchanged	Worsened	*P*-value [a)]
Lead-in period	Placebo	481	16.4% (79)	82.7% (398)	0.8% (4)	0.8017
	Ramelteon	489	17.4% (85)	81.4% (398)	1.2% (6)	
Week 1	Placebo	479	31.9% (153)	66.8% (320)	1.3% (6)	0.9116
	Ramelteon	488	33.4% (163)	63.7% (311)	2.9% (14)	
Week 2	Placebo	472	37.7% (178)	60.8% (287)	1.5% (7)	0.0881
	Ramelteon	475	42.7% (203)	56.6% (269)	0.6% (3)	

Response rate (%) (N)
a) Wilcoxon's rank sum test

In a phase II/III study (5.3.5.1-2.1, CCT002) and a long-term treatment study (5.3.5.2-1, OCT002), next-day residual effects[27)] on daytime function (ability to function, alertness, ability to concentrate) were evaluated. The results were as shown in the following table and no residual effects were observed. Also in foreign clinical studies (5.3.5.4-7, EC301; 5.3.5.1-4, EC302), daytime function (ability to function, alertness, ability to concentrate) were assessed. There were no differences between the Ramelteon and placebo groups and no residual effects were observed.

Table. Daytime function over time in phase II/III study (5.3.5.1-2.1, CCT002) and long-term treatment study (5.3.5.2-1.1, OCT002)

	Dose group	Ability to function	Alertness	Ability to concentrate	Total
Phase II study (CCT002)					
Baseline	Placebo	4.04 ± 0.62 (380)	4.09 ± 0.57 (380)	4.12 ± 0.59 (380)	4.08 ± 0.57 (380)
	Ramelteon 4 mg	4.07 ± 0.66 (372)	4.12 ± 0.62 (372)	4.17 ± 0.64 (372)	4.12 ± 0.62 (372)
	Ramelteon 8 mg	4.10 ± 0.60 (378)	4.13 ± 0.56 (378)	4.17 ± 0.58 (378)	4.14 ± 0.56 (378)
Week 1	Placebo	3.99 ± 0.63 (380)	4.01 ± 0.59 (380)	4.03 ± 0.61 (380)	4.01 ±0.59 (380)
	Ramelteon 4 mg	4.08 ± 0.64 (371)	4.11 ± 0.61 (371)	4.14 ± 0.63 (371)	4.11 ± 0.61 (371)
	Ramelteon 8 mg	4.10 ± 0.64 (378)	4.14 ± 0.61 (378)	4.18 ± 0.63 (378)	4.14 ± 0.61 (378)
Week 2	Placebo	3.97 ± 0.64 (376)	4.01 ± 0.58 (376)	4.03 ± 0.60 (376)	4.00 ± 0.59 (376)
	Ramelteon 4 mg	3.93 ± 0.64 (364)	3.98 ± 0.61 (364)	4.00 ± 0.62 (364)	3.97 ± 0.60 (364)
	Ramelteon 8 mg	3.94 ± 0.65 (368)	3.99 ± 0.62 (368)	4.02 ± 0.64 (368)	3.98 ± 0.62 (368)
Long-term treatment study (OCT002)					
Lead-in period		4.14 ± 0.74 (190)	4.17 ± 0.66 (190)	4.20 ± 0.67 (190)	4.17 ± 0.67 (190)
Week 1		4.11 ± 0.80 (190)	4.15 ± 0.73 (190)	4.20 ± 0.73 (190)	4.15 ± 0.73 (190)
Week 4		3.97 ± 0.77 (184)	3.99 ± 0.72 (184)	4.02 ± 0.73 (184)	3.99 ± 0.73 (184)
Week 8		3.91 ± 0.78 (183)	3.92 ± 0.75 (183)	3.94 ± 0.77 (183)	3.92 ± 0.75 (183)
Week 12		3.87 ± 0.81 (172)	3.91 ± 0.77 (172)	3.92 ± 0.78 (172)	3.90 ± 0.78 (172)
Week 16		3.81 ± 0.80 (164)	3.83 ± 0.77 (164)	3.86 ± 0.78 (164)	3.83 ± 0.77 (164)
Week 20		3.78 ± 0.74 (160)	3.82 ± 0.70 (160)	3.84 ± 0.71 (160)	3.81 ± 0.71 (160)
Week 24		3.82 ± 0.73 (158)	3.85 ± 0.71 (158)	3.85 ± 0.71 (158)	3.84 ± 0.71 (158)

Mean ± SD (N)

Furthermore, in a foreign clinical study, the residual effects of 8 mg of Ramelteon and zopiclone on driving performance were evaluated (5.3.5.4-6, EC103). As a result, the geometric mean of the standard deviation of the lateral position (cm) was 18.31 with placebo, 20.49 with Ramelteon, and 21.24 with zopiclone and the ratio of Ramelteon to placebo and the ratio of zopiclone to placebo were 1.119 and 1.160, respectively. There were statistically significant differences ($P < 0.001$ for both, ANOVA), but the standard deviation of the lateral position was smaller with Ramelteon compared to zopiclone, suggesting that Ramelteon has an equal or smaller residual effect.

27) Daytime ability to function, alertness, and ability to concentrate were assessed using a 7-point scale ranging from "1: Excellent" to "7: Extremely poor."

Then, the incidence of adverse events related to residual effects[28] was assessed in Japanese and foreign clinical studies (short-term studies [Japan, 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; Overseas, Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-11, TL025; Reference data 5.3.5.1-12, TL069], long-term studies [Japan, 5.3.5.2-1.1, OCT002; Overseas, 5.3.5.1-4, EC302; 5.3.5.2-2, TL022; 5.3.5.4-10, TL032]). As a result, no adverse events related to residual effects were reported in the short-term Japanese clinical studies, and the incidence of disturbance in attention was 0.17% (2 of 1176 subjects) in the placebo group and 0.27% (5 of 1872 subjects) in the Ramelteon group in the short-term foreign clinical studies, indicating that the incidence was low in both groups. No adverse events related to residual effects were reported in the long-term Japanese clinical study, and the incidence of decreased activity was 0.1% (2 of 1498 subjects) and the incidence of disturbance in attention was 0.2% (3 of 1498 subjects) in the long-term foreign clinical studies. The events reported in the long-term studies all occurred within 4 weeks of treatment initiation.

PMDA considers as follows:
Improvement of next-day functioning by Ramelteon was not demonstrated in the Japanese phase III study (5.3.5.1-3.1, CCT003). Although no apparent residual effect was observed in either the Ramelteon or placebo group in other Japanese clinical studies (5.3.5.1-2.1, CCT002; 5.3.5.2-1.1, OCT002) and the foreign clinical studies (5.3.5.4-7, EC301; 5.3.5.1-4, EC302), there was a residual effect of Ramelteon compared with placebo on driving performance in the foreign clinical study (5.3.5.4-6, EC103), albeit the inability to compare with zopiclone. Therefore, considersing that Ramelteon may produce a residual effect, it is necessary to provide a caution, as is the case of currently marketed hypnotics (this information has already been included in the “Important Precautions” section of the package insert). The impact of Ramelteon on next-day functioning needs to be further investigated via post-marketing surveillance.

4.(iii).B.(3) Safety of Ramelteon

4.(iii).B.(3).1) Neurological and psychiatric adverse events (somnolence, headache, insomnia exacerbated, depression)

PMDA asked the applicant to explain the incidences of neurological and psychiatric adverse events.

The applicant explained as follows:
The data from Japanese and foreign placebo-controlled studies (Japan, 5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; Overseas, Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-11, TL025; Reference data 5.3.5.1-12, TL069) were pooled separately, and neurological and psychiatric adverse events were summarized as shown in the following table. The events with a higher incidence in the Ramelteon group than in the placebo group were somnolence, headache, etc. in both Japan and overseas. In the foreign studies, insomnia exacerbated, depression, etc. were reported, but most of the observed events were mild in severity and there were no differences in severity between the placebo and Ramelteon groups.

[28] Adverse events were identified by the MedDRA Preferred Terms (PTs): “decreased activity,” “disturbance in attention,” and “change in sustained attention”

Table. Incidences of neurological and psychiatric adverse events in Japanese and foreign clinical studies

	Japan		Overseas	
	Placebo	Ramelteon	Placebo	Ramelteon
N	923	1674	1176	1872
Overall	23.5 (217)	34.6 (580)	40.6 (478)	48.3 (904)
Somnolence	1.3 (12)	3.6 (60)	2.3 (27)	5.3 (99)
Headache	1.8 (17)	2.3 (39)	7.1 (83)	9.5 (177)
Dizziness	0.1 (1)	0.8 (13)	3.4 (40)	4.0 (74)

Incidence (%) (No. of subjects with event)

As Ramelteon had an effect on sleep architecture as measured by PSG in Japanese and foreign clinical studies [see "4.(iii).B.(1).3) Effects of Ramelteon on sleep parameters other than sleep latency"], PMDA asked the applicant to explain the frequencies of neurological and psychiatric adverse events (somnolence, headache, insomnia exacerbated, depression) over time and then explain their association with alteration of sleep architecture by Ramelteon.

The applicant explained as follows:

In a Japanese long-term treatment study (5.3.5.2-1.1, OCT002), 3 events of somnolence were reported by 3 subjects and 8 events of headache were reported by 7 subjects, but somnolence occurred by Week 8 and headache occurred by Week 12. In foreign long-term treatment studies (5.3.5.1-4, EC302; 5.3.5.2-2, TL022; 5.3.5.4-10, TL032), the frequencies of somnolence, headache, insomnia exacerbated, and depression over time were as shown in the following figure, and somnolence and headache occurred mostly in the early phase of treatment and insomnia exacerbated and depression were found sporadically, regardless of duration of treatment. In the foreign clinical study (5.3.5.1-4, EC302), despite the fact that alteration of sleep architecture by Ramelteon persisted up to 6 months of treatment, adverse events of somnolence and headache occurred from the early phase of treatment, and there was also no trend towards an increased frequency of insomnia exacerbated or depression with prolonged treatment. Therefore, although the association between alteration of sleep architecture by Ramelteon and safety during treatment with Ramelteon is unclear, there should be little safety concern.

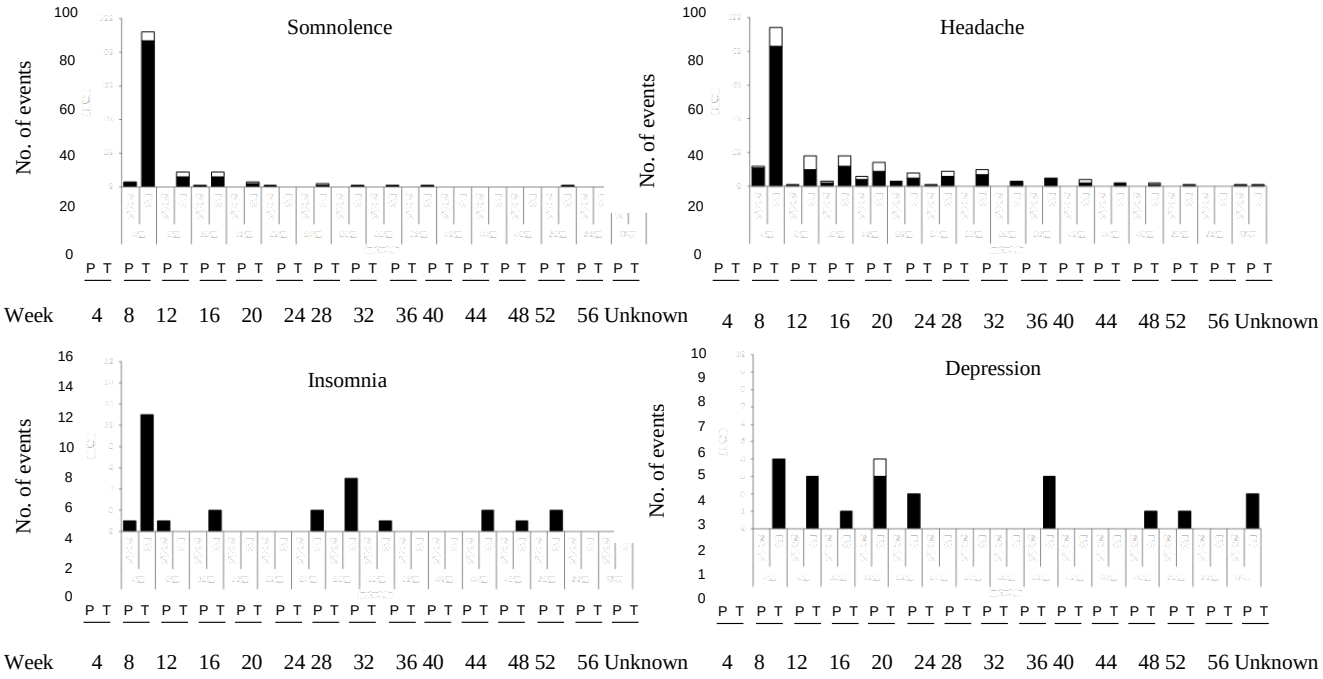

Figure. Frequencies of somnolence, headache, insomnia exacerbated, and depression over time in foreign long-term treatment studies
(P: Placebo group, T: Ramelteon group, ■: First occurrence, □: Re-occurrence)

Furthermore, in foreign clinical studies (Reference data 5.3.5.1-9, TL021; 5.3.5.1-4, EC302), the incidence of adverse events by the presence or absence of an effect on sleep architecture (≥2% increase for Stage 1 and Stage 2, ≥2% decrease for Stage 3/4) was as shown in the following table. There was no consistent trend in the incidence of adverse events according to the presence or absence of an effect on sleep architecture. Also, no major differences were observed for the nature of the reported events.

Table. Incidence of adverse events by presence or absence of an effect on sleep architecture in foreign clinical studies
(Reference data 5.3.5.1-9, TL021; 5.3.5.1-4, EC302)

		Effect on Stage 1		Effect on Stage 2		Effect on Stage 3/4	
		Present	Absent	Present	Absent	Present	Absent
TL021	Placebo	47.6 (10/21)	48.2 (53/110)	39.6 (19/48)	53.0 (44/83)	37.5 (15/40)	52.7 (48/91)
	Ramelteon 8 mg	59.0 (23/39)	48.5 (48/99)	40.6 (28/69)	62.3 (43/69)	45.6 (26/57)	55.6 (45/81)
	Ramelteon 16 mg	44.8 (13/29)	57.5 (61/106)	47.7 (31/65)	61.4 (43/70)	46.8 (22/47)	59.1 (52/88)
EC302	Placebo	52.5 (21/40)	49.7 (90/181)	44.8 (30/67)	52.6 (81/154)	47.7 (21/44)	50.8 (90/177)
	Ramelteon 8 mg	50.0 (19/38)	52.9 (99/187)	55.4 (56/101)	50.0 (62/124)	54.3 (50/92)	51.1 (68/133)

Incidence (%) (No. of subjects with event/No. of subjects evaluated)

PMDA asked the applicant to compare the incidence of somnolence between Ramelteon and other hypnotics, and explain impaired consciousness following the administration of Ramelteon and whether a warning in the package insert is needed because it is stated in the warnings section of the package insert for currently marketed hypnotics that “a twilight state or parasomnia (somnambulism, etc.) may occur after taking the drug. Also prior to falling asleep or during interim periods of wakefulness, memory may be impaired.”

The applicant explained as follows:

In Japanese clinical studies (5.3.5.1-1, CCT001; 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003) and foreign clinical studies (Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-11, TL025; Reference data

5.3.5.1-12, TL069), the incidences of adverse events possibly related to somnolence, a twilight state, parasomnia (somnambulism, etc.), and memory impairment prior to falling asleep or during interim periods of wakefulness[29] were as shown in the following table. Although somnolence occurred more frequently in the Ramelteon group compared with the placebo group, no major differences in the incidence were noted for other events, and most of the events were mild to moderate in severity.

Table. Incidences of adverse events related to impaired consciousness in Japanese and foreign placebo-controlled studies

	Japan		Overseas	
	Placebo	Ramelteon	Placebo	Ramelteon
N	923	1674	1176	1872
Somnolence	1.3 (12)	3.6 (60)	2.3 (27)	5.3 (100)
Syncope	0 (0)	0 (0)	0.3 (3)	0.1 (2)
Lethargy	0 (0)	0 (0)	0.3 (3)	0.7 (14)
Sedation	0.2 (2)	0.1 (1)	0.2 (2)	0.4 (8)
Disturbance in attention	0 (0)	0 (0)	0.2 (2)	0.3 (5)
Judgment impaired	0 (0)	0 (0)	0 (0)	0.1 (1)
Abnormal dreams	0 (0)	0 (0)	0.3 (3)	0.5 (10)
Somnambulism	0 (0)	0 (0)	0.2 (2)	0 (0)
Memory impairment	0 (0)	0 (0)	0.3 (3)	0.8 (15)
Amnesia	0 (0)	0 (0)	0.1 (1)	0.1 (1)

Incidence (%) (No. of subjects with event)

In zopiclone- or zolpidem-controlled, foreign clinical studies (5.3.5.4-6, EC103; 5.3.5.4-7, EC301; 5.3.5.4-8, TL060), the incidences of adverse events possibly related to somnolence, a twilight state, parasomnia (somnambulism, etc.), and memory impairment prior to falling asleep or during interim periods of wakefulness[29] were as shown in the following table. The incidence of events suggestive of transient anterograde amnesia tended to be higher in the active control group. Also, taking account of the pharmacological mechanism of action of Ramelteon, a warning in the package insert should be unnecessary.

[29] Adverse events were identified by the following PTs under the MedDRA High Level Terms (HLTs) of “disturbances in consciousness NEC,” “mental impairment (excl. dementia and memory loss),” “abnormal sleep-related events,” and “memory loss (excl. dementia)”:

loss of consciousness, consciousness fluctuating, altered state of consciousness, depressed level of consciousness, somnolence, sopor, stupor, syncope, lethargy, sedation, postictal state, disturbance in attention, cognitive disorder, judgement impaired, abnormal dreams, confusional arousal, sleep inertia, abnormal sleep-related event, sleep terror, sleep sex, sleep paralysis, sleep talking, somnambulism, loss of dreaming, memory impairment, retrograde amnesia, amnesia, amnestic disorder, global amnesia, and anterograde amnesia

Table. Incidences of adverse events related to impaired consciousness in foreign active-controlled studies (5.3.5.4-6, EC103; 5.3.5.4-7, EC301; 5.3.5.4-8, TL060)

	EC103			EC301			TL060		
	P group	T group	ZP group	P group	T group	ZP group	P group	T group	ZL group
N	30	30	30	94	88	93	33	33	33
Depressed level of consciousness	0 (0)	10.0 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Somnolence	33.3 (10)	66.7 (20)	73.3 (22)	1.1 (1)	9.1 (8)	8.6 (8)	0 (0)	6.1 (2)	6.1 (2)
Lethargy	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Sedation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3.0 (1)	0 (0)	0 (0)
Disturbance in attention	20.0 (6)	40.0 (12)	23.3 (7)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)	0 (0)
Abnormal dreams	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)	0 (0)
Memory impairment	0 (0)	3.3 (1)	23.3 (7)	0 (0)	1.1 (1)	1.1 (1)	0 (0)	0 (0)	0 (0)
Anterograde amnesia	0 (0)	0 (0)	6.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence (%) (No. of subjects with event)
P group: Placebo group, T group: Ramelteon group, ZP group: Zopiclone group, ZL group: Zolpidem group

Furthermore, the results of evaluation of the effect of Ramelteon on memory function in the above clinical studies (5.3.5.4-6, EC103; 5.3.5.4-7, EC301; 5.3.5.4-8, TL060) were as shown in the following table and Ramelteon had little or no effect on most parameters compared to zopiclone or zolpidem.

Table. Memory function tests in foreign active-controlled studies (5.3.5.4-6, EC103; 5.3.5.4-7, EC301; 5.3.5.4-8, TL060)

		Placebo	Ramelteon	Active control[a)]
EC103				
Sternberg Memory Scanning Test[b)]	Reaction time (ms)	536.1 ± 20.8 (30)	565.6 ± 20.8 (30)	584.1 ± 20.8 (30)
	Difference from placebo [95% CI]	-	29.5 [4.0, 55.0]	48.1 [22.6, 73.6]
	P-value	-	0.024	< 0.001
	Percentage of errors (%)	4.2 ± 0.8 (30)	5.2 ± 0.8 (30)	5.2 ± 0.8 (30)
	Difference from placebo [95% CI]	-	1.0 [-0.2, 2.2]	1.0 [-0.2, 2.2]
	P-value	-	0.109	0.109
Word learning test[b)]	Immediate recall	13.5 ± 0.3 (30)	13.5 ± 0.3 (30)	13.1 ± 0.3 (30)
	Difference from placebo [95% CI]	-	-0.0 [-0.6, 0.6]	-0.4 [-1.1, 0.2]
	P-value	-	1.000	0.171
	Delayed recall	12.2 ± 0.5 (30)	11.1 ± 0.5 (30)	10.1 ± 0.5 (30)
	Difference from placebo [95% CI]	-	-1.1 [-2.1, -0.1]	-2.1 [-3.1, -1.1]
	P-value	-	0.032	< 0.001
	Recognition score	13.9 ± 0.2 (30)	13.7 ± 0.2 (30)	13.6 ± 0.2 (30)
	Difference from placebo [95% CI]	-	-0.2 [-0.8, 0.4]	-0.3 [-0.9, 0.3]
	P-value	-	0.579	0.319
	Recognition time (ms)	713.6 ± 32.0 (30)	722.1 ± 32.0 (30)	767.4 ± 32.0 (30)
	Difference from placebo [95% CI]	-	8.5 [-48.8, 65.8]	53.7 [-3.6, 111.0]
	P-value	-	0.768	0.065
EC301				
Memory recall test[c)]	Pre-dose score[e)]	8.2 ± 2.4 (91)	8.6 ± 2.5 (85)	8.6 ± 2.4 (84)
	Post-dose score[e)]	6.3 ± 1.9 (91)	6.4 ± 2.2 (85)	5.5 ± 2.1 (84)
	Change	-2.0 ± 0.2	-2.1 ± 0.2	-3.0 ± 0.2
	Difference from placebo [95% CI]	-	-0.1 [-0.6, 0.4]	-1.0 [-1.5, -0.4]
	P-value	-	0.706	< 0.001
TL060				
Memory recall test[d)]	Immediate recall	5.40 ± 0.28 (32)	5.56 ± 0.28 (32)	4.10 ± 0.28 (33)
	Difference from placebo [95% CI]	-	0.16 [-0.62, 0.95]	-1.30 [-2.08, -0.52]
	P-value	-	0.683	0.002
	Delayed recall	4.00 ± 0.46 (32)	4.16 ± 0.46 (32)	3.59 ± 0.46 (33)
	Difference from placebo [95% CI]	-	0.16 [-0.55, 0.88]	-0.41 [-1.12, 0.29]
	P-value	-	0.650	0.247

Least square mean ± SE (N)
a) Zopiclone for EC103 and EC301, Zolpidem for TL060
b) 9.5 hours post-dose
Mixed effect model with treatment, sequence, and period as fixed effects and subject as a random effect
c) 1.5 hours pre-dose and 1.5-2 hours post-dose on Night 14
Mixed effect model with baseline as a covariate, treatment, sequence, and period as fixed effects, and subject as a random effect
d) After middle of the night awakening
Mixed effect model with baseline as a covariate, treatment, sequence, period, and center as fixed effects, and subject as a random effect
e) Arithmetic mean ± SD

PMDA considers as follows:
Since most of the neurological and psychiatric adverse events associated with Ramelteon were mild in severity and there was also no trend towards an increase with prolonged treatment, there seems to be no major problem. However, a caution about somnolence associated with Ramelteon should be included in the package insert, such as the ones used in currently marketed hypnotics [see "4.(iii).B.(2) Impact of Ramelteon on next-day functioning"].

The possibility of impaired consciousness associated with Ramelteon can not be ruled out. However, taking into account that the pharmacological mechanism of action of Ramelteon is different from those of other hypnotics and that zopiclone and zolpidem produced impairment, but Ramelteon did not produce impairment in memory function tests in the foreign clinical studies (5.3.5.4-6, EC103; 5.3.5.4-7, EC301; 5.3.5.4-8, TL060), a warning or a contraindication like that for other hypnotics, is unnecessary at present. Moreover, although the effect of Ramelteon on sleep architecture and the safety of long-term treatment with Ramelteon are unlikely to become a clinically relevant problem at present, as the intended population for Ramelteon includes the elderly, the safety of Ramelteon needs to be further investigated via post-marketing surveillance.

4.(iii).B.(3).2) Adverse events related to a muscle-relaxing effect
PMDA asked the applicant to explain the incidences of adverse events related to muscle relaxation.

The applicant explained as follows:
In Japanese and foreign short-term studies (Japan, 5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; Overseas, Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-11, TL025; Reference data 5.3.5.1-12, TL069) and Japanese and foreign long-term studies (Japan, 5.3.5.2-1.1, OTC002; Overseas, 5.3.5.1-4, EC302; 5.3.5.2-2, TL022; 5.3.5.4-10, TL032), the incidences of adverse events related to muscle relaxation[30] were as shown in the following table. Ramelteon is unlikely to have a risk of inducing muscle relaxation.

Table. Incidences of adverse events related to muscle relaxation in Japanese and foreign clinical studies

	Short-term studies				Long-term studies		
	Japan		Overseas		Japan	Overseas	
	Placebo	Ramelteon	Placebo	Ramelteon	Ramelteon	Placebo	Ramelteon
N	862	1609	1176	1872	190	288	1498
Hypotonia	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)
Weakness	0 (0)	0 (0)	0.2 (2)	0.5 (9)	0 (0)	0 (0)	0.3 (5)
Asthenia	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)
Muscular weakness	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence (%) (No. of subjects with event)

PMDA considers as follows:
Taking into account that the incidences of adverse events related to muscle relaxation were low in Japanese and foreign clinical studies and that the mechanism of action of Ramelteon is different from those of currently marketed hypnotics [see "3.(i).B.(1) Mechanism of action of Ramelteon"], muscle relaxation is

[30] Adverse events were identified by the MedDRA PTs: "hypotonia," "weakness," "asthenia," and "muscular weakness."

unlikely to occur following the administration of Ramelteon. There is no need to include a caution about this matter in the package insert at present, but the occurrence of adverse events related to a muscle-relaxing effect needs to be identified via post-marketing surveillance.

4.(iii).B.(3).3) Rebound insomnia and withdrawal syndrome after discontinuation of Ramelteon

PMDA asked the applicant to explain the occurrence of rebound insomnia and withdrawal syndrome after discontinuation of Ramelteon.

The applicant explained as follows:

In Japanese clinical studies (5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; 5.3.5.2-1.1, OCT002), subjective sleep latency (sSL) during the lead-in period, at the end of the treatment period, and during the run-out period (mean of 7 days) was as shown in the following table. There was no trend towards greater sSL after discontinuation of Ramelteon than during the lead-in period and there was no adverse event related to insomnia. A similar trend was observed also in foreign clinical studies. Thus, rebound insomnia is unlikely to occur after discontinuation of Ramelteon.

Table. sSL during the lead-in period, at the end of treatment period, and during the run-out period in Japanese clinical studies (minutes) (5.3.5.1-2.1, CCT002; 5.3.5.1-3.1, CCT003; 5.3.5.2-1.1, OCT002)

	Phase II/III study (CCT002)[a)]			Phase III study (CCT003)		Long-term treatment study (OCT002)
	Group L	Group M	Group H	Placebo	Ramelteon 8 mg	
Lead-in period	79.86 ± 42.35 (380)	83.28 ± 44.84 (372)	77.46 ± 44.30 (378)	77.42 ± 30.22 (482)	77.13 ± 30.81 (489)	72.86 ± 50.41 (190)
At the end of treatment period	47.87 ± 30.29 (368)	53.85 ± 38.83 (355)	46.90 ± 37.86 (360)	59.62 ± 29.13 (478)	56.95 ± 31.37 (478)	38.70 ± 29.12 (158)
Run-out period	49.08 ± 33.40 (366)	55.02 ± 35.78 (349)	47.68 ± 36.35 (352)	57.14 ± 29.90 (471)	55.89 ± 29.80 (475)	41.67 ± 31.58 (114)

Mean ± SD (N)

a) Groups L, M, and H received placebo, Ramelteon 4 mg, and Ramelteon 8 mg, respectively, on Days 1-14 and Ramelteon 4 mg, Ramelteon 8 mg, and Ramelteon 16 mg, respectively, on Days 15-28.

In Japanese clinical studies, changes in the Benzodiazepine Withdrawal Syndrome Questionnaire (BWSQ) total score[31)] at the end of the run-out period from the end of the treatment period were assessed. As a result, the change in BWSQ total score was 0.0 ± 0.87 (mean ± SD) in the Ramelteon 4 mg group, -0.1 ± 1.33 in the Ramelteon 8 mg group, and -0.1 ± 0.81 in the Ramelteon 16 mg group in a phase II/III study (5.3.5.1-2.1, CCT002) and -0.1 ± 0.59 in a Japanese long-term treatment study (5.3.5.2-1.1, OCT002) and there was no withdrawal syndrome and no adverse events related to withdrawal syndrome were reported. A similar trend was observed also in foreign clinical studies. Thus, withdrawal syndrome is unlikely to occur after discontinuation of Ramelteon.

PMDA considers as follows:

The presented Japanese and foreign study data indicate that rebound insomnia and problematic withdrawal syndrome as experienced with currently marketed hypnotics are unlikely to occur after discontinuation of Ramelteon. However, the occurrence of these events needs to be identified via post-marketing surveillance.

4.(iii).B.(3).4) Dependence and abuse potential

31) A 20-item questionnaire that records the severity of withdrawal symptoms, e.g. dysaesthesia that are considered typical to benzodiazepines. Each symptom is scored on a 3-point scale (0 = absent, 1 = moderate, 2 = severe).

Prolonged use of currently marketed hypnotics has been shown to produce dependence. PMDA asked the applicant to explain the dependence and abuse potential of Ramelteon.

The applicant explained as follows:
Non-clinical studies suggested that Ramelteon produces no dependence [see "3.(iii).A.(7) Other toxicity studies"]. In foreign clinical studies in subjects with a history of drug dependence (Reference data 5.3.5.4-1, TL014; 5.3.5.4-2, TL015), the dependence potential of Ramelteon was assessed using triazolam as a positive control. As a result, dose-related responses of drug liking etc. were seen with triazolam at doses from 0.25 mg (the clinical dose) to 0.75 mg (3 times the clinical dose) while no major differences were found between Ramelteon and placebo at doses up to 20 times the recommended clinical dose (160 mg). Therefore, it is unlikely that Ramelteon causes any dependence in clinical use. Ramelteon was approved as the first hypnotic that is not controlled under the Controlled Substance Act in the US. Also, according to post-marketing safety information (during the period from July 22, 2005 [International Birth Date] to July 21, 2009), there is no report suggesting abuse potential. The dependence potential of Ramelteon was assessed using dependence questionnaires in Japanese clinical studies. As a result, there was no evidence of dependence in both a phase II/III study (5.3.5.1-2.1, CCT002) and a long-term treatment study (5.3.5.2-1.1, OCT002).

PMDA considers as follows:
Based on the non-clinical and clinical study data, Ramelteon at the clinical dosage produces no dependence, unlike currently marketed hypnotics. The dependence potential of Ramelteon needs to be assessed via post-marketing surveillance.

4.(iii).B.(3).5) Effects of Ramelteon on endocrine function

As melatonin has been reported to inhibit the release of ACTH, glucocorticoids, and gonadotropins [Preslock JP et al, *Endocr Rev*, 1984;5: 282-308, see "3.(iii).B. *Outline of the review by PMDA*"], PMDA asked the applicant to explain the effects of Ramelteon on endocrine function.

The applicant explained as follows:
In a Japanese long-term treatment study (5.3.5.2-1.1, OCT002) and foreign clinical studies (Reference data 5.3.5.4-9, TL031; Reference data 5.3.5.4-10, TL032; Reference data 5.3.5.2-2, TL022) in which blood hormone levels (pituitary hormones [adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin], thyroid hormones [triiodothyronine (T_3), thyroxine (T_4), free thyroxine], adrenal hormone [cortisol], gonadal hormones [estradiol, total testosterone, free testosterone])[32)] were measured, changes in hormone levels in the same direction at multiple timepoints were prolactin increase only. Prolactin levels over time in the Japanese long-term treatment study (5.3.5.2-1.1, OCT002) were as shown in the following table. and prolactin levels tended to increase following the administration of Ramelteon, but 1 case of prolactin abnormal (increase) only was reported as an adverse event related to prolactin increased in this study.

32) In the foreign long-term treatment study (5.3.5.2-2, TL022), prolactin or estradiol was not measured.

Table. Blood prolactin levels (ng/mL) over time in Japanese long-term treatment study (5.3.5.2-1.1, OCT002)

	Overall		Male subjects		Female subjects	
	Blood level	*P*-value[a)]	Blood level	*P*-value[a)]	Blood level	*P*-value[a)]
Lead-in period	11.42 ± 5.69 (47)	-	8.63 ± 2.93 (13)	-	12.49 ± 6.15 (34)	-
Week 1	13.36 ± 6.23 (47)	0.0126	9.68 ± 3.97 (13)	0.1868	14.76 ± 6.40 (34)	0.0282
Week 4	12.41 ± 6.22 (45)	0.1662	8.58 ± 1.84 (13)	0.9401	13.97 ± 6.71 (32)	0.1476
Week 8	13.04 ± 8.56 (45)	0.1293	9.31 ± 3.97 (13)	0.4986	14.55 ± 9.47 (32)	0.1689
Week 12	14.74 ± 11.83 (42)	0.0568	9.84 ± 4.35 (12)	0.1960	16.70 ± 13.30 (30)	0.0900
Week 16	13.06 ± 7.94 (42)	0.0889	10.28 ± 4.23 (12)	0.0228	14.17 ± 8.83 (30)	0.2406
Week 20	13.70 ± 7.61 (40)	0.0193	10.86 ± 3.62 (11)	0.0425	14.78 ± 8.46 (29)	0.0676
Week 24	13.11 ± 7.02 (40)	0.0244	11.15 ± 5.29 (11)	0.0741	13.86 ± 7.52 (29)	0.1146

Mean ± SD (N)
a) One-sample t test

In a Japanese phase II/III study (5.3.5.1-2.1, CCT002) and a Japanese phase III study (5.3.5.1-3.1, CCT003), adverse events related to prolactin increased[33)] reported were dysmenorrhoea (Phase II/III study [5.3.5.1-2.1, CCT002], 0.3% [1 of 380 subjects] in the group L, 1.3% [5 of 372 subjects] in the group M, and 0.5% [2 of 378 subjects] in the group H; Phase III study (5.3.5.1-3.1, CCT003), 0.2% in the placebo group and 0.2% in the Ramelteon group [1 of 482 subjects and 1 of 489 subjects, respectively]) and most of the events were mild in severity. In foreign long-term studies (5.3.5.2-2, TL022; 5.3.5.4-10, TL032; 5.3.5.1-4, EC302), adverse events related to prolactin increased were as shown in the following table. Although adverse events related to prolactin increased dose-dependently in Study TL022 (5.3.5.2-2), different doses were selected for different age groups in Study TL022 (5.3.5.2-2) (8 mg for ≥65 years; 16 mg for <65 years) and dose-dependency can not be assessed. According to foreign post-marketing data (during the period from July 22, 2005 [International Birth Date] to July 27, 2009), 57 adverse events possibly related to prolactin increased were reported and the incidence based on the estimated number of patients exposed to Ramelteon (during the period from July 22, 2005 [International Birth Date] to July 21, 2009, 355512 patient-years) was 1.60 per 10000 patient-years and 1 case of vaginal haemorrhage and 1 case of breast mass were reported as serious adverse drug reactions, which were both transient and resolved following the discontinuation of Ramelteon. Based on the above, although Ramelteon is unlikely to be associated with adverse events related to prolactin increased, as blood prolactin increased has been reported with Ramelteon, if symptoms related to prolactin increased (menstrual abnormality, galactorrhoea, decreased libido, etc.) occur during treatment with Ramelteon, appropriate therapeutic measures such as discontinuing administration of the drug should be taken, which will be incorporated into the package insert. The mechanism of blood prolactin increased associated with Ramelteon is undefined.

33) Events related to blood prolactin changes (blood prolactin abnormal, blood prolactin decreased, blood prolactin increased) and events considered related to reproductive effects under the MedDRA SOCs of “reproductive system and breast disorders” and “endocrine disorders”

Table. Incidences of adverse events related to prolactin increased in foreign clinical studies

	TL022		TL032		EC302	
	Ramelteon 8 mg	Ramelteon 16 mg	Placebo	Ramelteon 16 mg	Placebo	Ramelteon 8 mg
N	248	965	65	57	223	228
All events related to prolactin increased	0.4 (1)	5.2 (50)	13.8 (9)	22.8 (13)	0.4 (1)	0 (0)
Amenorrhoea NOS	0 (0)	0.3 (3)	6.2 (4)	1.8 (1)	0 (0)	0 (0)
Breast discharge	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Breast engorgement	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dysfunctional uterine bleeding	0 (0)	0 (0)	0 (0)	1.8 (1)	0 (0)	0 (0)
Dysmenorrhoea	0 (0)	1.1 (11)	1.5 (1)	5.3 (3)	0 (0)	0 (0)
Erectile dysfunction NOS	0 (0)	0.2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Menstrual disorder NOS	0 (0)	1.8 (17)	3.1 (2)	1.8 (1)	0 (0)	0 (0)
Menstruation irregular	0 (0)	1.7 (16)	7.7 (5)	3.5 (2)	0 (0)	0 (0)
Premenstrual syndrome	0 (0)	0 (0)	1.5 (1)	0 (0)	0 (0)	0 (0)
Libido decreased	0.4 (1)	0.5 (5)	0 (0)	0 (0)	0.4 (1)	0 (0)
Prolactinoma	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Blood prolactin increased	0 (0)	0 (0)	0 (0)	10.5 (6)	0 (0)	0 (0)

Incidence (%) (No. of subjects with event)

PMDA considers as follows:

Although the possibility of prolactin increased following the administration of Ramelteon can not be ruled out, taking into account that most of the adverse events related to prolactin increased were mild in severity, if an appropriate caution statement is included in the package insert, there will likely be no major problem. The occurrence of adverse events related to prolactin increased etc. following the administration of Ramelteon needs to be further investigated via post-marketing surveillance.

4.(iii).B.(4) Reasons for refusal of authorization in the EU

A marketing authorization application for Ramelteon was submitted in the EU in March 2007. However, the Committee for Medicinal Products for Human Use (CHMP) of the EMA issued a negative opinion for granting a marketing authorization to Ramelteon in June 2008 and the application was withdrawn in September 2008. PMDA asked the applicant to explain the details of the regulatory review of Ramelteon in the EU.

The main issues discussed in the review in the EU were as follows:

(a) The efficacy of Ramelteon regarding sleep parameters other than sleep latency was not adequately demonstrated.

(b) The efficacy of Ramelteon was not evaluated in an active-controlled study and its effect of reducing sleep latency was undefined, and the efficacy of Ramelteon was demonstrated in sleep laboratory studies, but not adequately in an outpatient setting, i.e. at home.

(c) In Study EC302 (5.3.5.1-4), sleep latency was reduced over time even in the placebo group and the long-term efficacy of Ramelteon was not demonstrated.

Note that a Japanese phase III study (5.3.5.1-3.1, CCT003) was not complete at the time of submission in the EU and was not included in the clinical data package for authorization in the EU.

Concerning the above issues pointed out by the EMA, the applicant explained as follows:

(a) Although the claimed indication in the EU at the time of submission was “insomnia in patients 18 years and older,” as definite efficacy of Ramelteon regarding parameters other than sleep latency was not

demonstrated in clinical studies of Ramelteon, the proposed indication was changed to "insomnia characterised by difficulty falling asleep in patients 18 years and older" in the course of the regulatory review. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines the diagnostic criteria for insomnia based on symptoms, and indicates that patients with a predominant complaint of difficulty initiating sleep are also diagnosed with insomnia, which is also supported by the EU's guidance for the development of hypnotics (European Medicines Agency, *Clinical investigation of hypnotic medicinal products*, 1991). Therefore, in the case where the proposed indication is "insomnia characterised by difficulty falling asleep," the efficacy of Ramelteon in reducing sleep latency needs to be evaluated, but there is no need to go as far as to confirm the efficacy of Ramelteon regarding other sleep parameters. In foreign clinical studies (Reference data 5.3.5.1-7, TL005; Reference data 5.3.5.1-8, TL017; Reference data 5.3.5.1-9, TL020; Reference data 5.3.5.1-10, TL021; Reference data 5.3.5.1-11, TL025; 5.3.5.1-4, EC302), sleep parameters other than sleep latency over time were as shown in the following table. While the total sleep time (TST) was prolonged in some studies, no consistent results across measures (PSG or subjective assessment), timepoints, or studies were obtained. There were no apparent effects on wake time after sleep onset, the number of awakenings, or sleep quality.[34)] Improvement of sleep efficiency by Ramelteon was shown almost consistently.

Table. Differences in total sleep time (TST) between 8 mg of Ramelteon and placebo in foreign clinical studies (minutes) (FAS, LOCF)

Timepoint	TST as measured by PSG				Subjective assessment of TST					
	TL021	EC302	TL005	TL017	TL020	TL021	TL025	EC302	TL005	TL017
Days 1-2	-	-	12.6 ± 4.2	11.5 ± 4.2	-	-	-	-	9.8 ± 6.5	3.1 ± 5.4
Week 1	19.0 ± 5.5	15.4 ± 4.3	-	-	-1.2 ± 4.4	4.9 ± 5.1	7.3 ± 3.8	6.8 ± 5.2	-	-
Month 1 (Week 5)	5.6 ± 5.6	6.2 ± 4.3	-	-	2.8 ± 5.1	6.6 ± 6.0	4.3 ± 4.6	1.9 ±5.7	-	-
Month 3	-	3.2 ± 4.4	-	-	-	-	-	7.4 ± 5.9	-	-
Month 6	-	1.3 ± 4.6	-	-	-	-	-	-4.1 ± 6.1	-	-

Least square mean ± SE
-: Not applicable

Table. Differences in wake time after sleep onset between 8 mg of Ramelteon and placebo in foreign clinical studies (minutes) (FAS, LOCF)

Timepoint	Wake time after sleep onset as measured by PSG			Subjective assessment of wake time after sleep onset		
	TL021	TL005	TL017	TL021	EC302	TL017
Days 1-2	-	1.6 ± 3.5	-4.6 ± 3.6	-	-	5.5 ± 5.1
Week 1	-2.4 ± 4.0	-	-	-13.8 ± 6.2	2.89 ± 4.95	-
Month 1 (Week 5)	3.6 ± 4.2	-	-	-0.9 ±6.5	5.94 ± 5.25	-
Month 3	-	-	-	-	2.75 ± 5.01	-
Month 6	-	-	-	-	11.35 ± 5.39	-

Least square mean ± SE
-: Not applicable

Table. Differences in the number of awakenings between 8 mg of Ramelteon and placebo in foreign clinical studies (FAS, LOCF)

Timepoint	Number of awakenings as measured by PSG			Subjective assessment of number of awakenings					
	TL021	TL005	TL017	TL020	TL021	TL025	EC302	TL005	TL017
Days 1-2	-	0.6 ± 0.3	0.5 ± 0.3	-	-	-	-	-0.1 ± 0.2	0.3 ± 0.2
Week 1	0.4 ± 0.4	-	-	0.2 ± 0.1	0.0 ± 0.1	-0.0 ± 0.1	0.08 ± 0.20	-	-
Month 1 (Week 5)	0.4 ± 0.4	-	-	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.28 ± 0.16	-	-
Month 3	-	-	-		-		-0.18 ± 0.20	-	-
Month 6	-	-	-		-		0.12 ± 0.22	-	-

Least square mean ± SE
-: Not applicable

34) Sleep quality was rated on a 7-point scale (1 = Excellent, 2 = Very good, 3 = Good, 4 = Fair, 5 = Poor, 6 = Very poor, 7 = Extremely poor).

Table. Differences in sleep efficiency between 8 mg of Ramelteon and placebo in foreign clinical studies (%) (FAS, LOCF)

Timepoint	TL021	TL005	TL017
Days 1-2	-	2.6 ± 0.9	2.4 ± 0.9
Week 1	4.0 ± 1.1	-	-
Month 1 (Week 5)	1.3 ± 1.2	-	-

Least square mean ± SE
-: Not applicable

Table. Differences in sleep quality between 8 mg of Ramelteon and placebo in foreign clinical studies (FAS, LOCF)

Timepoint	TL020	TL021	TL025	EC302	TL005	TL017
Days 1-2	-	-	-	-	-0.1 ± 0.1	-0.0 ± 0.1
Week 1	0.1 ± 0.1	-0.0 ± 0.1	-0.0 ± 0.1	-0.12 ± 0.09	-	-
Month 1 (Week 5)	-0.0 ± 0.1	-0.0 ± 0.1	-0.1 ± 0.1	0.01 ± 0.09	-	-
Month 3	-	-		-0.03 ± 0.09	-	-
Month 6	-	-		-0.00 ± 0.09	-	-

Least square mean ± SE
-: Not applicable

In the Japanese phase III study (5.3.5.1-3.1, CCT003), there was improvement in subjective TST and the number of awakenings [see "4.(iii).B.(1).3) Effects of Ramelteon on sleep parameters other than sleep latency"] and the PGI and sleep quality also improved in the Ramelteon group compared with the placebo group. The efficacy of Ramelteon regarding other sleep parameters as well as sleep latency has been demonstrated.

(b) Ramelteon has a benefit of not having an anxiolytic or muscle-relaxing effect, unlike currently marketed hypnotics, and it is inappropriate to compare sSL using a currently marketed hypnotic as a control [see "4.(iii).B.(1).2).(a) Clinical significance of sSL and LPS improvement and the optimal dose of Ramelteon"]. In the review by the EMA, Study TL020 (Reference data 5.3.5.1-9), Study TL025 (Reference data 5.3.5.1-11), and Study CCT002 (5.3.5.1-2.1) that assessed sSL at home were evaluated as pivotal studies, and Study TL021 (Reference data 5.3.5.1-10) or Study EC302 (5.3.5.1-4) that assessed LPS in a sleep laboratory was not evaluated as a pivotal study. However, since objectively measured LPS is also important for the evaluation of the efficacy of hypnotics, placebo-controlled, double-blind comparative studies with a treatment duration of ≥4 weeks using sleep latency (LPS and sSL) as the primary endpoint (5.3.5.1-4, EC302; Reference data 5.3.5.1-9, TL021; Reference data 5.3.5.1-10, TL020; Reference data 5.3.5.1-11, TL025) should be evaluated as pivotal studies. The results of these studies are as shown in the following figure and the superiority of Ramelteon to placebo for LPS was demonstrated in all studies. Also, there was a trend towards improvement in sSL, but inter-study variability was large and there were no significant differences in some studies.

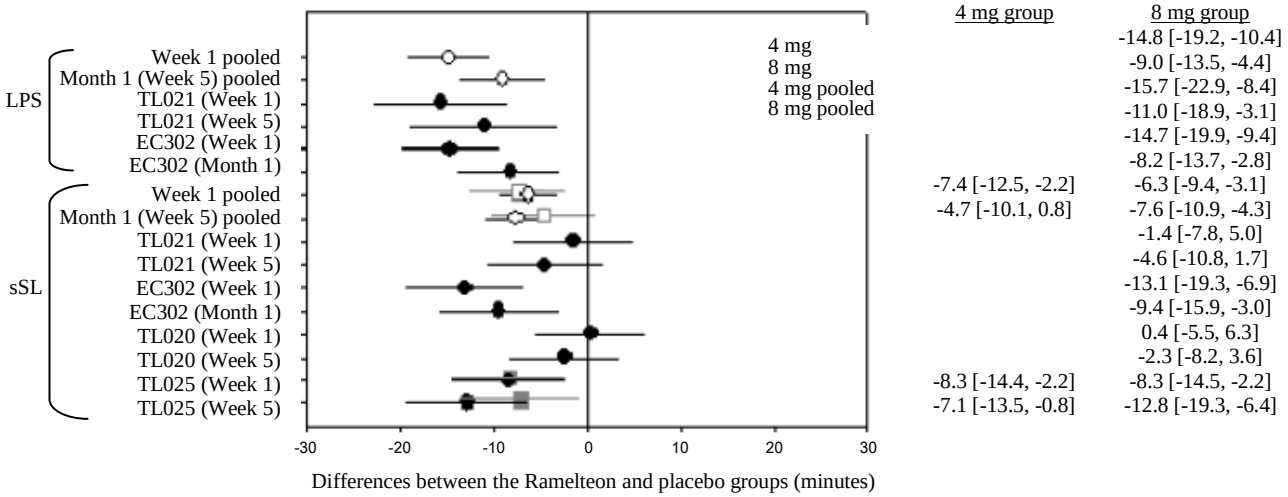

Figure. Effect of Ramelteon in reducing sleep latency in foreign clinical studies (difference from placebo)

In Japan, a phase II study (5.3.5.1-1, CCT001) demonstrated the efficacy of Ramelteon in reducing LPS and the phase III study (5.3.5.1-3.1, CCT003) demonstrated the superiority of Ramelteon to placebo for the primary endpoint of sSL over the first week of treatment at home. Therefore, it is considered that the efficacy of Ramelteon has been demonstrated.

(c) As pointed out by the the EMA, sleep latency was reduced over time even in the placebo group in Study EC302 (5.3.5.1-4). However, also in clinical studies of other hypnotics, due to improvement of symptoms in the placebo group, the effect size tended to diminish over time (Krystal AD et al, *Sleep*, 2003;26: 793-799, Walsh JK et al, *Sleep Medicine*, 2000;1: 41-49). In Study EC302 (5.3.5.1-4), for the primary endpoint of LPS, a statistically significant difference between Ramelteon and placebo was observed even at 6 months of treatment and there was a trend towards improvement in the secondary endpoint of sSL as well. Thus, the long-term efficacy of Ramelteon has been demonstrated. In the Japanese phase III study (5.3.5.1-3.1, CCT003), while Ramelteon was superior to placebo for sSL at Week 1 but not at Week 2, Ramelteon continued to be superior to placebo also at Week 2 among patients with good compliance. Also in a long-term treatment study (5.3.5.1-2.1, OCT002), though it was an uncontrolled study, the efficacy of Ramelteon was maintained up to 6 months.

Taking account of the above, the applicant explained their view again on the issues pointed out by the EMA in the course of the review. However, as the EMA's opinion remained unchanged, the applicant decided to withdraw the application in the EU and review the submission data package and then consider resubmission of the application in the EU. As for regulatory submission in Japan, Japanese clinical study data etc., which were not reviewed in the EU, are also included in the data package and these data have demonstrated the efficacy and safety of Ramelteon in Japanese patients.

PMDA considers as follows:

The Japanese phase III study (5.3.5.1-3.1, CCT003), which was not included in the application dossier for the marketing authorization in the EU, has demonstrated the efficacy and safety of Ramelteon and foreign

clinical studies also do not deny the efficacy of Ramelteon. Also regarding safety, although it is necessary to watch for new information, there have been no significant events at present. Based on these findings, the benefits of Ramelteon outweigh its risks.

4.(iii).B.(5) Positioning of Ramelteon in the treatment of insomnia and proper use

PMDA asked the applicant to explain the positioning of Ramelteon in the treatment of insomnia.

The applicant explained as follows:

It has been reported that currently marketed hypnotics are associated with a high incidence of withdrawal syndrome or rebound insomnia after a dose reduction or interruption of the drug and therefore, most patients need the continuous use of the drug and few patients can successfully discontinue the use of the drug with a psychiatrist's guidance and the duration of treatment is likely to be prolonged (Uchimura N et al., *Research on guideline for hypnotic discontinuation, Development of guidelines for the diagnosis and treatment of sleep disorders and its empirical research, 1999 to 2001 Research Report, MHLW-sponsored research project on psychiatric/neurological disorders*). It has been reported that the risk of falling is several times higher in patients treated with BZD than in untreated patients (Herings RM et al, *Arch Intern Med*, 1995;155: 1801-1807), which has been reported to lead to femur fractures (Sorock GS et al, *Arch Intern Med*, 1988;148: 2441-2444). Since Ramelteon has a low risk of rebound insomnia, withdrawal syndrome, and adverse events related to a muscle relaxing effect [see "4.(iii).B.(3).2) Adverse events related to a muscle-relaxing effect and 4.(iii).B.(3).3) Rebound insomnia and withdrawal syndrome after discontinuation of Ramelteon"], Ramelteon is considered safer than currently marketed hypnotics. Taking into account that the efficacy of Ramelteon was higher in patients with a shorter duration of disease and patients previously untreated with hypnotics, etc. in a Japanese phase II/III study (5.3.5.1-2.1, CCT002) see "4.(iii).B.(1).1).(a) Justification for the screening criteria regarding subjective sleep latency during the lead-in period"]. The applicant considers that Ramelteon is positioned as a treatment for patients who are at the initial stage of insomnia.

PMDA considers as follows:

Given that currently marketed hypnotics are associated with rebound insomnia and withdrawal syndrome and have dependence and abuse potential, Ramelteon offers a new option for the treatment of insomnia and has clinical significance. However, since the Japanese phase II/III study (5.3.5.1-2.1, CCT002) failed to demonstrate the efficacy of Ramelteon in patients previously treated with hypnotics and the phase III study (5.3.5.1-3.1, CCT003) did not enroll a patient previously treated with BZD etc., it should be stated in the package insert that the efficacy of Ramelteon in this patient population has not been established. In addition, since the Japanese phase III study (5.3.5.1-3.1, CCT003) failed to demonstrate the efficacy of Ramelteon at Week 2 and suggested the efficacy of Ramelteon at Week 2 among "patients with good compliance" only, the package insert should state that after the initiation of Ramelteon treatment, its efficacy and safety should be monitored continuously, administration without careful consideration should be avoided, and patients should also be instructed to improve their lifestyle [see "4.(iii).B.(1).2).(b) Efficacy of long-term use of Ramelteon"]. In light of the pharmacological mechanism of action of Ramelteon and the outcome of the review by the EMA, the indication statement needs to be further reviewed, but the details will be

determined, taking account of comments from the Expert Discussion.

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, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (Phase II/III study: CCT002, Phase III study: CCT003, long-term treatment study: OCT002). As a result, it was found that using the revised written information reflecting changes to the protocol-specified exclusion criteria, a new written consent to continue to participate in the ongoing trial had not been obtained from subjects at some clinical trial sites. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of Ramelteon in the treatment of insomnia has been demonstrated and its safety is acceptable in view of its observed benefits. Since the mechanism of action of Ramelteon is different from those of currently marketed hypnotics, Ramelteon offers a new option for the treatment of insomnia and has clinical significance. Measures for the proper use of Ramelteon (the duration of treatment, patient education on lifestyle, etc.), the way of cautioning against the use of Ramelteon in patients previously treated with hypnotics, and other measures for proper use will be finalized, taking account of comments from the Expert Discussion. It is necessary to continue to investigate, via post-marketing surveillance, the following issues: the safety of Ramelteon in the elderly, the occurrence of adverse events related to a muscle-relaxing effect, the occurrence of rebound insomnia and withdrawal syndrome, dependence potential, and the effects of Ramelteon on endocrine system.

Ramelteon may be approved, if the results of the Expert Discussion lead to the conclusion that there are no particular problems.

Review Report (2)

January 12, 2010

I. Product Submitted for Registration

[Brand name] Rozerem Tablets 8 mg
[Non-proprietary name] Ramelteon
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] February 29, 2008

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).

PMDA's conclusions as described in the Review Report (1) were supported at the Expert Discussion, but PMDA conducted an additional review of the following points and took necessary actions.

(1) Proper use of Ramelteon

PMDA considers that in order to promote the proper use of Ramelteon, taking into account the fact that Ramelteon has a different mechanism of action from currently marketed hypnotics, it is important to diagnose candidate patients appropriately and at the same time, for both healthcare professionals, such as physicians, and patients to understand that the lifestyle also needs to be improved. Thus, PMDA asked the applicant to explain measures to promote the proper use of Ramelteon, e.g., cooperation with the relevant academic societies and the development of educational material.

The applicant explained as follows:

The following measures will be taken to provide information to prescribing physicians: the differences in the mechanism of action between Ramelteon and currently marketed hypnotics and the appropriate patient population for Ramelteon will be explained; educational material describing the need to improve lifestyle will be developed; and since Ramelteon may be prescribed also by physicians other than insomnia specialists, a workshop for general practitioners will be held to provide information on the treatment of insomnia and the proper use of Ramelteon. In order to provide information to patients, the following tools are planned to be distributed: materials that describe the mechanism of action of Ramelteon and the guidance on lifestyle improvement and its necessity etc., and diaries to record the rhythm of daily life and sleep. Thus, it will be easier for patients to discuss the treatment effect with their physicians by utilizing their diaries etc.

PMDA accepts the above, but considers that it is important to take these measures promptly, diagnose candidate patients appropriately, and ensure that both healthcare professionals, such as physicians, and patients understand that Ramelteon should be used with guidance on lifestyle improvement while monitoring its treatment effect.

(2) Post-marketing surveillance

PMDA requested the applicant to conduct post-marketing surveillance of patients with sleep-onset insomnia to investigate the relationship of gender or age with the efficacy and safety of Ramelteon, the relationship of the presence or absence of prior therapy with hypnotics or the duration of disease with the efficacy and safety of Ramelteon, the impact of Ramelteon on next-day functioning, the occurrence of impaired consciousness and neuropsychiatric adverse events, and the occurrence of withdrawal symptoms, rebound insomnia, abuse and dependence, and muscle relaxation such as staggering, which are problematic events associated with currently marketed hypnotics, etc.

The applicant explained as follows:

A drug use-results survey of patients with sleep-onset insomnia, with a target number of patients of 3000 and an observation period consisting of a 4-week treatment and a 2-week follow-up for each patient, will be conducted. The efficacy of Ramelteon in improving difficulty falling asleep will be assessed at 2 weeks of treatment, and the guidance on lifestyle improvement and compliance with the guidance etc. will be checked at 4 weeks of treatment or at the end of treatment. In addition, in order to evaluate the long-term safety and efficacy of Ramelteon in patients for whom continued treatment with Ramelteon is considered to be necessary and who have completed the drug use-results survey, a special drug use-results survey with a target number of patients of 200 and an observation period consisting of a 6-month treatment and a 2-week follow-up for each case will be conducted. Items to be investigated include the following: the relationship of gender or age with the efficacy and safety of Ramelteon, the relationship of the presence or absence of prior therapy with hypnotics or the duration of disease with the efficacy and safety of Ramelteon, the occurrence of impaired consciousness (memory impairment during interim periods of wakefulness, etc.), residual effects of Ramelteon, the impact of Ramelteon on next-day functioning, the occurrence of neuropsychiatric adverse events, the occurrence of withdrawal symptoms, rebound insomnia, abuse and dependence, muscle relaxation such as staggering, which are problematic events associated with currently marketed hypnotics, the effects of Ramelteon on blood prolactin levels and the occurrence of associated adverse events, the relationship of caffeine or alcohol use and smoking habit with the efficacy and safety of Ramelteon, and the efficacy and safety of Ramelteon when coadministered with CYP1A2 inhibitors.

PMDA accepts the above, but considers that the surveillance should be conducted promptly, the efficacy and safety of Ramelteon in patients with sleep-onset insomnia should be confirmed, and the information on the obtained results should be provided to the clinical practice appropriately.

(3) Ramelteon indication, intended population, and duration of treatment

Although the submitted clinical study data have shown improvement in sleep latency, PMDA considers that the appropriate indication of Ramelteon should be "improvement of sleep-onset insomnia," as Ramelteon did not produce clear improvement in total sleep time or the number of awakenings. This PMDA's opinion was supported by the expert advisors. Therefore, PMDA instructed the applicant to modify the proposed indication accordingly, and the applicant accepted it.

PMDA considers that the following information should be provided appropriately: a Japanese phase II/III study (5.3.5.1-2.1, CCT002) failed to demonstrate the efficacy of Ramelteon in patients previously treated with hypnotics; the efficacy and safety of Ramelteon in patients with psychiatric conditions (schizophrenia, depression, etc.) have not been studied and are not defined; and a Japanese phase III study (5.3.5.1-3.1, CCT003) failed to demonstrate the efficacy of Ramelteon at Week 2. Since this PMDA's opinion was supported by the expert advisors, PMDA instructed the applicant to include the following statement in the "Precautions of Indications" section of the package insert: "The efficacy of Ramelteon in patients previously treated with other hypnotics such as benzodiazepines and the efficacy and safety of Ramelteon in patients with prior or current psychiatric conditions (schizophrenia, depression, etc.) have not been established. Ramelteon should be administered to these patients with caution after balancing the expected therapeutic benefits against the potential risks and fully determining the need for Ramelteon" and include the following statement in the "Important Precautions" section of the package insert: "Prior to the use of Ramelteon, patients should be instructed to improve their lifestyle, and the efficacy of Ramelteon in improving difficulty falling asleep should be assessed at 2 weeks of treatment. If no efficacy is observed, treatment discontinuation should be considered and Ramelteon should not be administered without careful consideration. Then, the efficacy and safety of Ramelteon should be assessed periodically to determine the need for continued treatment." The applicant accepted it.

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and dosage and administration statements as shown below. The re-examination period is 8 years, the drug substance is classified as a powerful drug and the drug product is not classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]
Improvement of sleep-onset insomnia

[Dosage and administration]
The usual adult dose is 8 mg as Ramelteon taken orally at bedtime.