European Medicines Agency
Evaluation of Medicines for Human Use

London, 23 October 2008
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WITHDRAWAL ASSESSMENT REPORT

FOR

Ramelteon Takeda Global Research and Development Centre (Europe) LTD

International Non-proprietary Name: **ramelteon**

Procedure No. EMEA/H/C/000838

CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Takeda Global Research and Development Centre (Europe) Ltd. submitted on 1 March 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ramelteon, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 18 October 2006.

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication "Ramelteon is indicated for the treatment of primary insomnia"

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
Ramelteon has been given a Marketing Authorisation in the United States on 22 July 2005.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Barbara van Zwieten-Boot

Co-Rapporteur: Cristina Sampaio

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 1 March 2007.
- The procedure started on 21 March 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 June 2007.
- During the meeting on 16-19 July 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 3 October 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2007.
- During the CHMP meeting on 10-13 December 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 19 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 10 April 2008.
- During the CHMP meeting on 21-24 April 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP on 23 April 2008.

- During the meeting on 27-30 May 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Ramelteon on 30 May 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

This application concerns Ramelteon, film coated tablets for oral administration. The tablets are immediate release formulations.
Ramelteon is a selective agonist of the melatonin type 1 (MT1) and type 2 (MT2) receptors in the suprachiasmatic nucleus (SCN). Physiologically, these receptors are associated with biorhythm and sleep-wake rhythm, regulated by circadian excretion of endogenous melatonin.

The originally sought indication was for:
the treatment of primary insomnia in adults.

Following discussion at the CHMP, the applicant proposed to narrow down the indication to the treatment of sleep latency, and to limit the duration of treatment to five weeks:
Treatment of primary insomnia characterised by difficulty falling asleep in patients 18 years and older.

The dose recommendation is 4 or 8 mg given 30 minutes before bedtime.

DSM-IV-TR defines Primary Insomnia as a complaint consisting of difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month (criterion A) that causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion B). The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia (criterion C) or mental disorder (criterion D). The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (criterion E).

Current pharmacologic treatments for insomnia involve mainly GABAergic mechanisms: most currently prescribed sleep agents are benzodiazepine receptor agonists (BZRAs), which induce sleep by binding to the benzodiazepine receptor site of the GABA-A receptors. The use of these compounds is limited to a short time interval due to risk of dependence.

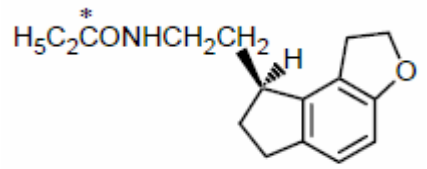
2.2 Quality aspects

Introduction

The medicinal product is a film-coated tablet with a new active substance Ramelteon, in two dosage strengths: 4 mg and 8 mg. It is an immediate release dosage form and the core consists of standard excipients (lactose, maize starch, hydroxypropylcellulose and magnesium stearate) as defined in section 6.1 of the SPC. The product is presented in transparent PVC/Al blisters.

Active Substance

Ramelteon INN is a chiral tetrahydro-indenofuran derivative, purified as the S-isomer, freely soluble in organic solvents but less soluble in water.



* -Indicates the carbon-14 label site.

Structure of the active substance
(S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide

Site of labelling (see structure).		
Isomerism.	no	
Molecular weight.	259.34	
Solubility in water.	0.21 mg/mL	
Pka.	-0.84 (computer simulation)	
Distribution coefficient.	320 (octanol/water)	
Solubility in other solvents.	Benzyl alcohol	440 mg/mL
	Methanol	300 mg/mL
	Dimethylsulfoxide	290 mg/mL
	Ethanol	200 mg/mL
	Octanol	90 mg/mL
	Acetonitrile	68 mg/mL
	Diethyl ether	6.9 mg/mL
Stability.		
Possible chirality and its consequences.	The S-form is included. A major metabolite (M-II) is a diastereoisomer. Only the (2S,8S) is formed in humans. This metabolite has been tested separately in monkeys.	

- **Manufacture**

The synthesis is a 4-step process. Starting materials are characterised and controlled to maintain the purity of the resulting active substance. The chiral centre is introduced during synthesis and process investigations demonstrate the satisfactory retention of this centre resulting in the S-isomer.
The active substance is purified by recrystallisation and micronised. The molecular structure has been confirmed by a wide range of spectroscopic methods, and there is no evidence of polymorphism.

Concerning impurities, a range of theoretical impurities has been described and those that are actually found have been isolated, investigated and the proposed limits have been justified and qualified.
Process validation studies have been performed with three production scale batches, manufactured at the proposed sites, according to the proposed synthesis.

Batch analytical data confirm the satisfactory uniformity of the process with regard to chemical and physical characteristics of the active substance.

- **Specification**

The specification includes tests for assay (non chiral HPLC), content of R-isomer (chiral HPLC), a range of related impurities by HPLC, heavy metals, residual solvents and particle size distribution, etc.

An acceptable number of production scale material manufactured at the proposed sites are available. The results are within the specification limits and indicate satisfactory uniformity and control of the manufacturing process.

- **Stability**

Stability studies have been carried out at 25°C/60%RH and 40°C/75%RH also stress degradation studies (50°C, 60°C, 25°C/93%RH) and ICH photostability studies (3000 Lx) option1 were conducted.

X-ray diffraction studies were additionally performed to check for potential solid-state transitions.
Forced degradation studies were also conducted in aqueous solutions at pH 1.1-12.8 at 60°C, with severe illumination and also in strong acid, strong base and 3%H2O2 at 60°C to e.g. elucidate the degradation routes of the drug substance.

Results indicate that some degradation products have been encountered in aqueous solution. The methods for related substances-degradation products/enantiomer/assay are sufficiently stability indicating. In conclusions a satisfactory re-test period has been agreed. The drug substance is not hygroscopic, but is light labile. Chirality and polymorphic form are not affected by storage within the re-test period.

Medicinal Product

- **Pharmaceutical Development**

The main factor influencing development has been the limited aqueous solubility of the active substance, although considering the small dose, this is not a major problem. Following synthesis the particle size of the active substance is reduced, and the effect of particle size on dissolution has been studied. These studies allow a mean particle size to be defined, suitable for further processing in the manufacture of the product. Ramelteon is slightly sensitive to light and has a bitter taste. Therefore, film-coating was applied, using conventional excipients.

Two excipients of potential animal origin are used in the manufacture of ramelteon tablets: magnesium stearate and lactose monohydrate. It is certified that magnesium stearate used will be of plant origin only, and it is certified that lactose monohydrate used is sourced from milk collected under the same conditions as for human consumption.

- **Manufacture of the Product**

The process is a standard mixing, granulation, lubrication, film-coating process that has been well-validated with regard to critical sub-processes.

- **Product Specification**

The product specification includes relevant tests with justified limits for appearance, identification of active, assay, related substances, content uniformity and dissolution.
Analytical control methods have been suitably validated. The dissolution test demonstrates satisfactory discriminatory properties.

- **Stability of the Product**

In addition to formal studies at 25°C/60%RH and 40°C/75%RH, the program also included stress degradation studies (50°C, 60°C, 25°C/93%RH) and photostability studies (ICH). In contrast to the active substance, no photo-instability was observed in the tablets – this is attributed to the film coat. In total, the results support the product shelflife and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The characterisation, manufacture and control of the active substance have been well documented in this application. Furthermore the pharmaceutical development, manufacture and control of the finished product have been carried out on a rational basis to arrive at a stable and uniform product that should perform consistently well in the clinic, from batch to batch.
At the time of the CHMP Opinion, a number of minor quality issues having no impact on the benefit/risk balance of the product were unresolved.

2.3 Non-clinical aspects

Introduction

In vitro primary pharmacology studies were conducted to evaluate the affinity of ramelteon and/or its metabolites for melatonin MT1, and MT2 receptors, and *MT3* binding sites and for effects on forskolin-stimulated cAMP production. *In vitro* studies were conducted using cells expressing native melatonin receptors and using human melatonin receptors stably transfected into Chinese hamster ovary (CHO) cells. *In vivo* primary pharmacology studies were conducted in monkeys and cats to evaluate the sleep-promoting effects of ramelteon and its primary diasterioisomer metabolite, M2 (2*S*,8*S*). The 2*S*,8*S* configuration predominates in rat and rabbit plasma and occurs exclusively in human serum when compared to the 2*R*,8*S* configuration.

Several *in vivo* studies were designed to evaluate secondary pharmacodynamic activities of ramelteon. Effects of ramelteon on the re-entrainment of the circadian rhythm of activity following a phase shift and on the performance of learned behaviours were examined in rats. The effect of ramelteon on plasma melatonin levels was studied in rats; pharmacologic characterization of the emetic liability of ramelteon and melatonin was conducted in monkeys.

In vitro and *in vivo* studies were conducted to evaluate the safety pharmacology of ramelteon and/or the primary M2 (2*S*,8*S*) metabolite on the central nervous, respiratory, cardiovascular, gastrointestinal, and renal systems. Ramelteon and M2 (2*S*,8*S*) were screened for binding to a broad panel of receptors and ion channels and for effects on enzymatic activity. The potential of ramelteon to produce physical dependence and drug abuse was examined in a series of rat and monkey studies. Pharmacodynamic interactions between ramelteon and diazepam were studied in a rota-rod task in mice.

GLP aspects

Pivotal nonclinical safety studies were conducted in accordance with the Good Laboratory Practices (GLP) regulations and were designed to comply with Organization for Economic Cooperation and Development (OECD), Japanese, and International Conference on Harmonisation (ICH) guidelines current at the time the studies were initiated. Non-pivotal toxicology studies and the supplementary carcinogenicity studies, which served to elucidate the mechanisms of tumourigenesis were not performed under GLP. This was accepted by the CHMP. Studies investigating dependence potential of ramelteon at the sponsor's facilities were conducted under GLP, but those performed at academic centres were conducted 'in the spirit of GLP'. As these studies were performed before the guideline on the nonclinical investigation of dependence potential of medicinal products came into effect, this was accepted by the CHMP.

Pharmacology

- Primary pharmacodynamics

Melatonin MT1/MT2 receptor agonistic activity
In binding assays using stably transfected CHO cells, ramelteon showed higher affinity then melatonin for the MT1 and MT2 receptors.
Ramelteon demonstrated full agonist activity against forskolin-stimulated cAMP production in CHO cells expressing MT1 and MT2 receptors.

Sleep promotion
Studies conducted in monkeys and cats evaluated the effects of ramelteon on sleep latency, duration, electroencephalogram (EEG) activity, and muscle relaxation. In monkeys, comparisons were made to the effects of melatonin and the benzodiazepine receptor agonist (BZRA) zolpidem. Overall, ramelteon reduced the time to sleep onset without producing abnormal EEG waveform, electromyographic (EMG), or electrooculographic (EOG) activity. The effects of melatonin in these models were less potent and shorter-lived than for ramelteon. The M2 metabolite was also active in promoting sleep in both monkeys and cats, although the effect was not dose-dependent in monkeys and, overall, M2 was considerably less potent in both species.

In monkeys, zolpidem had little effect on latencies to sleep onset and produced myorelaxation and an increase in high-frequency (30 Hz) EEG activity during sleep; neither ramelteon nor M2 affected these parameters.

No data on repeated administration were provided. The potential development of tolerance could not be ruled out since it cannot be excluded that ramelteon may have desensitising properties towards the melatonin receptors.

- Secondary pharmacodynamics

The Entrainment of Circadian Rhythms
The re-entrainment of activity (alignment of endogenous circadian rhythms to the to the daily light-dark cycle) after an 8- hour phase shift (advance) was studied in Wistar rats treated daily with vehicle, ramelteon, or melatonin for 14 days using a paradigm that has been reported to be sensitive to the actions of melatonin. Overall, all groups treated with ramelteon demonstrated more rapid re-entrainment of wheel running compared with vehicle. Melatonin also promoted activity re-entrainment, although it was 10-fold less potent than ramelteon.

Effects on Mnemonic Processes and Other Pharmacodynamic Effects of Ramelteon
Treatment of rats with high doses of ramelteon (up to 30 mg/kg) or melatonin (100 mg/kg) did not impair the animals' abilities to swim to or locate a hidden platform in the Morris water maze and did not affect the behaviour of the animals on the probe trial. In contrast, rats treated with triazolam or diazepam were impaired on both the hidden platform task and the probe trial, observations that are consistent with the literature for BZRAs.
In a separate study, animals were trained on an operant delayed-matching-to-position task, used to evaluate the effects of pharmacologic agents on an animal's ability to retain information in working memory. Neither ramelteon nor melatonin produced significant effects on task performance although diazepam and triazolam produced dose-dependent decreases in response accuracy.

- Safety pharmacology

Central Nervous System
Ramelteon was examined for effects on the CNS in mice, rats and cats. Observations can be summarised as follows:

- General CNS effects: slight sedation, enhanced pentobarbital-induced sleep times, and anticonvulsant activity, each occurring at a high dose of 100 mg/kg.
- Reduction of the percent of time cats demonstrated EEG arousal.
- Slight reduction of body temperature in monkeys at 200 mg/kg PO, but no effect in rats,
- Potentiation of barbiturate-induced sleep times, similar to the reported with melatonin. Studies have reported that this effect of melatonin was not antagonised either by benzodiazepine or cannabinoid receptor antagonists. Given these findings, the effects of ramelteon on barbiturate-induced sleep times are also unlikely to involve either benzodiazepine or cannabinoid receptors, a contention further supported by the results of secondary pharmacology studies demonstrating the selectivity and specificity of ramelteon for melatonin receptors.
- No potentiation of diazepam-induced impairments in the performance of mice on a rota-rod task at doses up to and including 30 mg/kg, PO. In contrast, melatonin and N-acetyl-5-HT both potentiated diazepam-induced impairments of rota-rod performance, suggesting that the interaction of ramelteon with BZRA is less probable.

Cardiovascular and Respiratory Systems

***In vitro* Cardiovascular preparations**

- In isolated Purkinje fibers significant reductions in action potential duration and in upstroke amplitude at high ramelteon concentrations (100 μmol/L) were observed.
- Neither ramelteon nor M-II (2*S*,8*S*) affected hERG currents expressed in HEK- 293 cells.

***In vivo* studies**

- In conscious dogs Ramelteon (66 mg/kg, PO) failed to affect respiration, heart rate, blood pressure or ECG parameters.
- In unrestrained, conscious monkeys equipped with telemetry devices, reductions in heart rates were accompanied by small increases in mean blood pressure in 2 of 3 monkeys after administration of 200 mg/kg ramelteon. The small increase in blood pressure produced by ramelteon at 200 mg/kg was suggested to reflect compensation for the reduction in heart rate.

Gastro-intestinal and urinary system

In vitro

High concentrations of ramelteon (100 µmol/L [26 µg/mL]) had slight inhibitory effects on the maximal contraction produced by acetylcholine and histamine in the isolated guinea pig ileum and slight inhibition of spontaneous motility in the isolated rabbit ileum.

In vivo

- Ramelteon (100 mg/kg, PO) produced a small but statistically significant enhancement in the intestinal transport of a semi-solid meal in rats
- Was without significant effect on gastric emptying in rats (100mg/Kg).
- Did not modify urine volume or electrolyte excretion in rats (up to 100 mg/Kg).
- In repeat dose toxicity studies in cynomolgus monkeys, an emetogenic effect was observed from 20 mg/kg/day, which was antagonized by melatonin antagonists.

The potential for ramelteon to cause **physical dependence or abuse liability** was studied in a reasonable set of studies in rats and monkeys. The study results did not point towards a potential for abuse or dependence for ramelteon.

- Pharmacodynamic drug interactions

The possibility for an interaction between ramelteon and benzodiazepines has been studied by analysing the effects of 3-30mg/ramelteon on rota-rod performance in diazepam-treated mice. No interaction was observed with ramelteon.

Pharmacokinetics

The pharmacokinetics of ramelteon were determined after oral or intravenous (IV) administration to mice, rats, dogs, and cynomolgus monkeys. Extensive pharmacokinetic evaluations were conducted in rats and monkeys, since these were the major species used in the toxicology program. The disposition of [^{14}C]ramelteon was studied in rats, monkeys, and humans. Plasma protein binding in rat, dog, monkey and human plasma was determined *in vitro*, and tissue distribution of radioactivity following a single oral dose of [^{14}C]ramelteon was evaluated in rats. Studies evaluated the absorption, distribution, metabolism and excretion of ramelteon and its metabolites. In addition, distribution studies of orally administered [^{14}C]ramelteon in the brain, pigmented eyeball, and placenta were conducted in rats. The biotransformation of ramelteon was investigated extensively *in vitro* and *in vivo* in rats, monkeys and humans. A milk excretion study and a pharmacokinetic drug interaction study with melatonin were also conducted with ramelteon in rats. Nonclinical pharmacokinetic and metabolism studies used formulations that were similar, or identical, to those used in toxicology and pharmacology studies.

Absorption

The following tabulated data summarise data from single dose pharmacokinetic studies:

Table 3.a Pharmacokinetics of Ramelteon Across Species Following Oral Administration

Species	Sex	Dose (mg/kg)	Formulation	Tmax (h)	Cmax (ng/mL)	AUC (ng·hr/mL)	BA (%)	Report Number
Rat	M	1	Susp(a)	0.25	17.5	21.3(b)	6.3	M-11-00781 [23]
Dog	M	1	Susp(a)	0.1	112	129 (c)	-	M-11-00642 [24]
Monkey	M	0.3	Susp(a)	0.33	0.525	0.414(b)	0.3	M-11-00782 [26]
Human	M	~0.23(d)	Tablet	0.75	3.89	0.325(b)	1.77(e)	EC003 [27]

(a) 0.5% methylcellulose (w/v) suspension.
(b) AUC(0-inf).
(c) AUC(0-24hr).
(d) 16 mg per person, assuming a body weight of 70 kg.
(e) Geometric least square mean value.

Table 3.b Pharmacokinetics of Ramelteon Across Species Following IV Administration

Species	Sex	Dose (mg/kg)	Vd (L/kg)	CL (mL/min/kg)	AUC(0-∞) (ng·hr/mL)	T1/2 (h)	Report Number
Rat	M	1	1.164	49.8	336.6	0.27	M-11-00781 [23]
Monkey	M	0.3	2.086	31	169.3	0.82	M-11-00782 [26]
Human	M	~0.03 (a)	2.04 (a)	13.0 (a)	18.2	1.80	EC003 [27]

(a) 2 mg administered as a 5-minute constant rate infusion (2 mL x 1 mg/mL IV dosing solution), assuming a body weight of 70 kg.

Oral and intravenous studies with low single doses of radiolabelled ramelteon in rats (1 mg/kg) and monkeys (0.03-1 mg/kg)) show a quick and high intestinal absorption of radiolabelled material (bioavailability of radiolabel: 70-80%). However, bioavailability of the parent compound was low (rats: 6-8%, monkeys: 0.3 – 30 %), indicating a high first-pass metabolism. Toxicokinetic data of much higher dose ranges show that also at high doses in mice (30-1000 mg/kg/day), rats (2.5-1000 mg/kg/day), monkeys (3-200 mg/kg/day) and pregnant rats (40-150 mg/kg/day) and pregnant rabbits (300 mg/kg/day), overall exposure to parent compound is also only a small fraction of the total exposure to ramelteon derived material. However exposure changes dose-dependently (superproportional at lower doses, changing to subproportional at higher doses). Therefore, the pharmacokinetic parameters based on the radio-label studies may not be applicable to doses tested in the toxicological studies. The most important human metabolite M-II is produced in appreciable concentrations in mice, rats and rabbits, but only to a limited extent and only at higher doses (> 3 mg/kg/day) in monkeys. The ratio of the 2S,8S form of M-II to the 2R,8S form of metabolite M-II was determined in monkeys, pregnant rats and pregnant rabbits. Most of M-II consisted of the 2S, 8S form, and in monkeys no sex difference was observed.
Data in Caco-2-cells reveal evidence for a high permeation of these monolayers, without the involvement of active processes. Experiments at low doses (1 mg/kg) with rat intestinal loop models showed quick and complete absorption from duodenum, jejunum and ileum. Toxicokinetic data (*in vivo* in mice, rats, rabbits and monkeys) also show quick absorption at higher doses, but it is not known whether absorption is also complete at these doses. Radiolabelled material present in portal vein plasma after absorption from a rat jejunal loop consisted for more than 90% of parent compound.

Distribution
Two studies examined *protein binding* of ^{14}C ramelteon *in vitro* in rats, dogs, monkeys and humans.
In the tested concentration range (0.01-1µg/ml), plasma protein binding of radiolabelled parent compound as measured by liquid scintillation counting appeared to be independent of drug concentration. Binding in human and rat plasma was similar, binding in monkey plasma was slightly lower and in dog plasma slightly higher.

Distribution into blood cells was similar in rat, monkey and man (about 20-35%), and much lower (0-3.4%) in dogs.

Tissue *distribution* in rats after *single administration* of a low dose of 14C ramelteon was examined in six studies. At a dose level of 1 mg/kg in rats show that radiolabelled material rapidly distributed over the body, penetrating well in brain tissues, and disappearing rapidly from all tissues. Concentrations in intestine (place of administration), and liver and kidney showed the highest peak values. Metabolites M2 and M2 (2S,8S) showed similar concentration profiles in plasma and brain tissue. Metabolite M4 was measured in brain tissue, but at much lower concentrations than in plasma. Although radiolabelled material reached higher concentrations in eyes of pigmented rats than in eyes of albino rats, disappearance from eye tissue was rapid and similar to that of other tissues.

Tissue *distribution after a repeated oral dose* of 1 mg/kg/day in rats showed that concentrations in all tissues increased during dosing periods of 21 and 35 days. At 4 and 8 weeks after the final dose, still detectable concentrations were found. After these washout periods, the highest concentrations were found in thyroid gland, lungs, spleen, kidneys, skin, fat tissue and femur. Part of this radioactivity may be due to incorporation of the 14C label in endogenous materials or in expired CO2 (lungs).

After oral administration of 14C labelled ramelteon to rats on gestation day 19, radioactivity rapidly *passes the placenta* and reaches concentrations in fetal plasma and tissue which exceed those in maternal plasma, but subsequently disappears quickly.

Studies on the *distribution after oral administration to mammary gland and milk of lactating rats* showed that concentrations of labelled ramelteon in mammary glands were similar to those in plasma. The concentration in milk exceeded that in plasma, but also quickly decreased from 4 to 24 hours.

Metabolism
Under *in vitro* conditions, CYP1A2 metabolises ramelteon to the important human metabolite M2. This is a stereoselective process mainly producing the (2S,8S) form of M2. In addition CYP1A2 produces M7 and M9, CYP3A4 produces M5 and M7, and both CYP2C8 and CYP2C19 also produce M7. *In vitro* evidence was provided indicating that M2 did not induce CYP3A4 and that – under *in vitro* conditions - the potential induction of the latter enzyme by ramelteon was much smaller than that of the positive control rifampicin.
In vivo studies with repeated daily oral gavage of ramelteon for one week in mice (dose range 30 – 1000 mg/kg/day) and rats (dose range 15 – 1000 mg/kg/day) resulted in induction of hepatic drug metabolising enzymes and increased liver weight

Studies on metabolite profiles in rats and monkeys after a dose of radiolabelled ramelteon, showed that the sum of the concentrations of the identified metabolites in plasma, brain, urine, faeces and bile constitutes only a small portion of the total radioactivity found in these matrices. A major part of the radioactivity was present in the form of other, unidentified, metabolites. Considering the place of the label at the propionamide group, it is plausible that part of the unidentified radioactivity is due to radiolabel present in small organic molecules (possibly incorporated into endogenous compounds or degradated to e.g. CO2), created after hydrolysis of the amide bond. Exhalation of about 5% of the radioactive dose, found in the excretion studies in rats supports this view. After hydrolysis of the propionamide group or other bond resulting in the loss of the labelled moiety, the remaining unlabelled portion of the molecule (the tetrahydro-indeno-furan moiety) may be present in concentrations equivalent to the unidentified part of the radioactivity. The concentrations may amount up to about 40% and 65% of total plasma radioactivity at 0.25 h after administration in rats and monkeys respectively and up to higher percentages (90% and more) at later time points in plasma and in urine, faeces, and bile.
The fate of this major part of the ramelteon molecule has not been documented in the submitted application.

Excretion
Excretion data following administration of single IV or oral doses of [14C] ramelteon to rats, monkeys and humans are summarized in the following Table:

Table 6.a Excretion of Total Radioactivity Across Species Following a Single Oral Dose of [^{14}C]ramelteon

Species	Sex	Route	(mg/kg)	Percent of Dose Excreted (%)			Report Number
				Urine	Feces	Total	
Rat	M	IV	1	59.0	32.3	96.8(a)	M-11-00789 [75]
	M	Oral	1	59.2	31.6	95.5(a)	M-11-00789 [75]
	M	Oral	1	61.3	32.2	98.8(a)	M-11-00049.001A [21]
Monkey	M	IV	0.3	78.2	12.3	90.5	M-11-00779 [77]
	M	Oral	0.3	77.2	11.3	88.5	M-11-00779 [77]
	M	Oral	1	80.2	9.9	90.1	M-11-00049.001A [21]
Human	M	Oral	0.23(b)	84.3	4.0	88.3	EC004 [28,29]

(a) Including small amount radioactivity recovered in expired air.
(b) Each subject (assuming 70 kg body weight) received 16 mg [^{14}C]ramelteon.

Both rats and monkeys excreted most of the dose in urines. In rats about 5% of radioactivity was excreted into air. Urinary excretion in rats was higher than in monkeys. There was no clear difference in excretion routes after oral and intravenous administration. In both species, excretion was almost complete after 72 h.
Following excretion into bile in rats, ramelteon-related radioactivity was shown to be re-absorbed significantly.

Pharmacokinetic interactions

Fluvoxamine, fluconazole and ketoconazole show clear inhibitory effects on metabolism of ramelteon by human hepatic microsomes. This has been confirmed by clinical data, where it was shown that concomitant administration of fluvoxamine leads to a 190-fold increase of ramelteon plasma AUC.

Toxicology

- Single dose toxicity

Repeat dose toxicity of ramelteon was evaluated in mice, rats and monkeys. Two studies of 4 weeks and 13 weeks duration were conducted in mice, eight studies, ranging from 2 weeks to 26 weeks duration, were conducted in rats, and six studies, ranging from 1 week to 39 weeks duration, were conducted in monkeys.
Ramelteon was well tolerated by rats and monkeys after oral administration at doses of less than 2000mg/kg. The acute toxicity is low. The lethal dose is much lower when administered intravenously, at around 60 mg/kg. Adverse effects seen at high doses indicate a central action of ramelteon, such as decreased locomotor activity, ataxic gait and hypothermia.

- Repeat dose toxicity

Most effects seen after treatment with ramelteon occurred at high doses, ranging from 40 mg/kg/day to 2000 mg/kg/day. Some of these effects, such as decreased locomotor activity, ataxic gait and hypothermia, were due to a central action of ramelteon. Convulsions occurred infrequently in rats and monkeys at high doses. Emesis occurred in monkeys from 20 mg/kg/day, which was antagonized by melatonin antagonists.

Ramelteon induced hepatic metabolism was evident in both mice and rats. *Adaptive responses of the liver* were measured by biochemical analysis of hepatic drug metabolizing enzyme activities and confirmed morphologically. In mice adaptive responses occurred at doses of 50 mg/kg/day and higher, while in rats they occurred at 40 mg/kg/day or higher. In mice, a dose of 50 mg/kg/day resulted in

increased liver weight, while enlarged liver, hepatocellular hypertrophy and increased liver enzymes and cholesterol occurred at 300 mg/kg/day or higher. In rats, enzyme activity was increased, as well as liver weight, at a dose of 150 mg/kg/day. Total cholesterol and triglycerides were increased starting at doses of 40mg/kg/day in females and 600 mg/kg/day in males. These adaptive liver responses may have led to changes observed in the thyroid gland and levels of thyroid hormones.
In monkeys, inconsistent increases in liver enzymes and liver weight were seen at doses of 200 mg/kg/day and higher.
Other effects after repeat dosing were seen in the adrenal glands and ovaries. Enlarged or increased weights of the adrenal gland were seen in rats at 150 mg/kg/day or higher and in monkeys at doses of 200 mg/kg/day or higher. Vacuolization of cells of the adrenal gland and ovaries occurred at 40 mg/kg/day or higher in rats, and at doses of 200 mg/kg/day or higher in monkeys. Decreased thymus weight was observed at high doses in Wistar rats but not in SD rats. In monkeys this occurred after two weeks of dosing, but not in studies of longer duration.

These effects occurred at high doses with exposure multiples of 500 or more when the animal AUC was compared to the human AUC, indicating no likely safety concern for humans. However, the strong interactions with Cyp-inhibitors (e.g. fluvoxamine, and perhaps food constituents) may lead to much higher concentrations in humans (190-fold increase in ramelteon AUC). Then the safety margin would be much smaller.
Since the partially active metabolite M2 is not formed sufficiently in monkeys, studies were performed using IV administration of this metabolite. There were no toxicological findings in these studies, indicating the low toxicity of this metabolite.

Overall, it was considered that the toxicological effects seen in animal studies are not likely to be relevant for human safety, as the exposures are at least 500 times higher then those in humans at a pharmacologically relevant dose, except in the event of a CYP-mediated interaction leading to higher human exposures.

- Genotoxicity

Genotoxicity was evaluated in microbial mutation, mouse lymphoma cell mutation test, CHO chromosomal aberration test, rat and mouse micronucleus *in vivo* study and a rat UDS *in vivo* study. Ramelteon is not genotoxic, although one *in vivo* chromosomal aberration test showed equivocal results, which could not be explained by cytotoxicity. Based on *in vivo* results, it was concluded that there was no genotoxic potential.

- Carcinogenicity

Two long-term studies (two year) were conducted, one in rats and one in mice, to assess the carcinogenicity potential of ramelteon.
The three types of tumour with increased incidence after treatment with ramelteon were Harderian gland adenomas in mice, liver tumours in mice and rats, and Leydig cell tumours in the testis of rats. As ramelteon is not genotoxic, this increase in tumour incidence is likely due to other, non-genotoxic, mechanisms. The mechanisms involved were not satisfactorily clarified. Adaptive liver responses could not fully explain the tumours observed at the lower doses in mice, whereas mechanistic studies involving hormone levels were performed at doses below those inducing liver tumours in rats. Increased melatonin levels were discussed in relation with harderian gland adenomas, but this mechanism was not substantiated with data. The Leydig cell tumours were considered to be due to a compensatory demand for testosterone leading to an increase in LH levels. Based on the fact that rat testosterone levels are more sensitive to change than humans and human Leydig cells have fewer LH receptors, it was considered unlikely that there is a human safety concern regarding this type of tumour. Toxicokinetic data indicate a large exposure margin for all neoplastic findings (1000 to 7500-fold). In conclusion, the relevance of these findings for human safety is considered low, although variation in human kinetics may affect the magnitude of the safety margins.

- Reproduction Toxicity

Standard *reproductive toxicity* studies were performed. Although fertility indices in males and females were not decreased, a slight increase of pre-implantation loss was observed after male treatment with 60 and 600 mg/kg/day. The effect was only present in the untreated female, possibly because the treatment period of the males was longer. In treated females, doses of 60 mg ramelteon and higher resulted in irregular cycles, the applicant hypothesizes that this is due to prevention of LH release. Measurements to confirm this hypothesis have not been performed.
In embryofetal studies in rats, some effects were observed (increased incidences of diaphragmatic hernia, lumbar rib, irregular shaped scapulae), however at exposures much higher than expected after human therapeutic exposure, which holds also true for the rabbit study. In rabbits, late abortions were observed at 60 (1 case) and 300 (2 cases) mg/kg, and also a total litter resorption in one 300 mg/kg/day rabbit. An increased incidence in lumbar rib was also observed in the rabbit study. However, the background (study control and historical control) values are also high. Furthermore, since safety margins are large, the toxicological relevance of these findings is further minimised.
In a pre- and postnatal study in rats, maternal toxicity was evident as decreased body weight, salivation, and increased adrenal weight. The NOAEL for these effects was 30 mg/kg. Maternal reproductive function was affected (poor lactation conditions: nipple development and/or nest behaviour disturbance). The NOAEL for these effects was 100 mg/kg. Developmental toxicity in offspring was evident from decreased body weight at the mid dose (NOAEL 30 mg/kg). At the high dose more severe toxicity was observed ((decreased viability index, delayed eruption of the lower incisors, delayed righting reflex, prolonged latency (failure to move in open field test) and diaphragmatic hernia. Again the adverse effects were only observed at exposure levels sufficiently above the expected human exposure.

- Local tolerance

Three local tolerance studies were conducted, one *in vitro* study on human blood cells to test haemolytic activity, and two *in vivo* studies in rabbits to assess intravenous and paravenous tolerance. Ramelteon showed to be well tolerated.

- Other toxicity studies

The development of physical *dependence* was studied in rats and monkeys following repeated treatment with ramelteon for 1 month and 1 year, respectively. The potential rewarding activity of ramelteon was examined in Wistar rats using a conditioned place preference paradigm, in two self-administration studies in rhesus monkeys using barbiturates as training drug and in two drug-discrimination studies in rhesus monkeys. From the data provided it is clear that ramelteon has a very low abuse liability. There is no evidence of withdrawal-related phenomena. Also with respect to self-administration behaviour the data do not suggest that ramelteon would exert a high abuse liability if any. Ramelteon does not generalize to midazolam in drug discrimination tests and does not interfere with flumazenil-precipitated withdrawal in diazepam-dependent animals.

No studies on antigenicity and immunotoxicity have been performed.

Ecotoxicity/environmental risk assessment

Ramelteon is very slightly soluble in water with logKOW= 2.5. A predicted environmental concentration in surface water (PECsurfacewater) for ramelteon of 0.002 µg/L, was initially based on first year tablet sales in the United States. Yet, further estimates of the potential Fpen based a.o. on the occurrence of insomnia and the degree of actual treatment with medicines, within the EU indicated the PECsurfacewater might exceed the trigger for a Phase II environmental risk assessment (ERA).

Discussion on the non-clinical aspects

Pharmacology
Ramelteon is a specific agonist of the melatonin MT1 and MT2 receptor. The sleep-promoting action consisted mainly in the reduction of sleep-latency. The pattern of the effects was clearly different from that of benzodiazepine-like compounds.
An important shortcoming of the dossier is the lack of data on the pharmacological effect of repeated administration since it can be expected that repeated administration will result in an adaptation of the effect.
The secondary pharmacodynamic data support the high selectivity of the product. However, with respect to the effect on hormones subject to a daily rhythm the dossier is very limited.
The safety pharmacology data suggest a pharmacodynamic interaction with barbiturates, but other data with benzodiazepines do not support a pharmacodynamic interaction with respect to sedative effects. Ramelteon is not expected to interfere with the cardiovascular, the respiratory, and the gastrointestinal and renal systems.

Pharmacokinetics
Ramelteon showed a quick and high intestinal absorption; however, it is subject to high first-pass metabolism resulting in a low bioavailability.
At lower doses repeated administration leads to increasing exposure, indicating accumulation. At higher doses repeated dosing results in decreasing exposure, indicating increased biotransformation due to enzyme induction.

After single dose, ramelteon rapidly distributed over the body, penetrating well in brain tissues. After repeat oral administration the highest concentrations were found in thyroid gland, lungs, spleen, kidneys, skin, fat tissue, and femur. It passes the placenta and is found in the breast milk.

Under *in vitro* conditions, CYP1A2 metabolises ramelteon to the most important human metabolite M2, which mainly consists of the 2S, 8S form.

Ramelteon is mainly excreted in urine.

Studies on metabolite profiles after a dose of radiolabelled ramelteon show that the sum of the concentrations of the identified metabolites in plasma, brain, urine, faeces and bile constitutes only a small portion of the total radioactivity found in these matrices. A major part of the radioactivity is present in the form of other, unidentified, metabolites. This could be due to the diversion of the labelled propionamide moiety, however the fate of the remaining part of the ramelteon molecule has not been documented.

Results from interaction studies showed that the effect of CYP1A2 inhibitors such as fluvoxamine resulted in a very large increase of ramelteon exposure (AUC increased more than 190 fold), but an insignificant effect on M2 levels. These results were confirmed in humans.

Toxicology
Ramelteon was well tolerated by rats and monkeys when administered as a single dose of up to 2000 mg/kg/day. The acute toxicity is low. Lethal doses after oral administration were between 600-2000 mg/kg/day for rats and higher than 2000 mg/kg/day for monkeys.

In studies on repeat dose toxicity of ramelteon, decreased locomotor activity and emesis were observed. Body temperature and heart rate were decreased in monkeys in one study.
At high doses decreases in food consumption and body weight occurred; convulsions occurred infrequently.

Liver adaptations: in mice and rats, high doses of ramelteon resulted in increased liver weight, enlarged liver, hepatocellular hypertrophy and increased liver enzymes and cholesterol. These adaptive liver responses may have led to changes observed in the thyroid gland and levels of thyroid hormones.

Other organs: enlarged or increased weights of the adrenal gland and decreased thymus weight were observed at high doses indicating no likely safety concern for humans.

Ramelteon is not *genotoxic*, although one *in vivo* chromosomal aberration test showed equivocal results, which could not be explained by cytotoxicity. The evidence is sufficient to conclude that there is no genotoxic potential, due to the negative *in vivo* results.

Three types of tumour with increased incidence after treatment with ramelteon are Harderian gland adenomas in mice, liver tumours in mice and rats, and Leydig cell tumours in the testis of rats. The increase in hepatic tumours coincided partly with an increase in hepatic enzymes, which is a known cause of carcinogenicity in rodents but not in humans. As Harderian gland does not exist in humans and the safety margins were in general very high, the *carcinogenic* potential of ramelteon is not of concern in humans.

Even though toxicology studies did not indicate *reproductive toxicity* concerns for humans, caution should still be exercised as the potential pharmacological modulation of hormones affecting pregnancy has not been investigated.

Studies on the *dependence potential* revealed that ramelteon has a very low abuse liability and there is no evidence of withdrawal-related phenomena.

No ramelteon-related effects were evident in *local tolerance* studies.

2.4 Clinical aspects

Introduction

Ramelteon is a selective agonist of the melatonin type 1 (MT1) and type 2 (MT2) receptors in the suprachiasmatic nucleus (SCN). Physiologically, these receptors are associated with biorhythm and sleep-wake rhythm, regulated by circadian excretion of endogenous melatonin. It has been licensed in the US since July 2005 as immediate release tablets under the name Rozerem and the dose recommendation is 4 or 8 mg given 30 minutes before bedtime.

DSM-IV-TR defines Primary Insomnia as a complaint consisting of difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month (criterion A) that causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion B). The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia (criterion C) or mental disorder (criterion D). The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (criterion E).
Insomnia, as defined by the DSM-IV-TR is a subjective clinical diagnosis. Since the patient's subjective experience of sleep difficulties is the basis for treatment seeking and for the diagnosis of insomnia, the evaluation of treatment efficacy is, likewise, mainly based on subjective reporting. Objective measures of sleep (polysomnographic measures) do not always correlate well with subjectively reported symptoms. Hence, assessments of treatment efficacy should reflect the patient's subjective experience while somnographic/objective measures if consistent with the subjective findings may be considered supportive (proof of concept studies). In addition, treatment efficacy needs to be shown on more that one component of insomnia, including sleep onset, sleep maintenance, sleep quality, and improvement in next day functioning.
Factors contributing to the onset of primary insomnia may be different from those that are responsible to its persistence. Persistence may be due to negative conditioning, e.g. negative association with sleep. Some individuals report better sleep in the laboratory than at home. Therefore, demonstration of efficacy should be in the context of the natural setting, where insomnia usually occurs.

Epidemiological studies suggest that the prevalence of insomnia increases with age and a shift in the prevalence of individual symptoms, with insomnia in young adults usually consisting of difficulty falling asleep while older individuals are more likely to experience difficulty in maintaining sleep and early morning awakening. Separate studies are necessary demonstrating efficacy and safety in adults and in the elderly, as elderly patients are more sensitive for CNS adverse events.

Research evidence further suggests that primary insomnia tends to be a chronic disorder. In this context, evidence for long-term efficacy and safety are necessary and issues of tolerability, rebound, and withdrawal need to be assessed. Dependence, and abuse liability needs to be assessed as well.

Current pharmacologic treatments for insomnia involve mainly GABAergic mechanisms: most currently prescribed sleep agents are benzodiazepine receptor agonists (BZRAs), which induce sleep by binding to the benzodiazepine receptor site of the GABA-A receptors. However, the use of these compounds is limited to a short time interval due to, among others, risk of dependence, tolerance, withdrawal, hangover and retrograde amnesia.

Melatonin was approved in primary insomnia for the improvement of sleep quality in adults who are >55 years old.

Guidelines

The current guideline for studies in insomnia, *Clinical Investigation of Hypnotic Medicinal Products* (3CC27A, http://www.emea.europa.eu/pdfs/human/ewp/3cc27aen.pdf) is focused on hypnotics. The need for an updated guideline, one that addresses other types of products, has been recently recognised, although an updated version is not available yet. Many of the topics discussed in the guideline for hypnotics and their solutions still apply.

The current guideline for hypnotics indicates that separate studies (pharmacodynamic and clinical) should be carried out in elderly subjects since the elderly form an important part of the target population. Pharmacodynamic studies should demonstrate the nature of the CNS effects (sleep architecture) as well as its onset and duration in relation to different doses. In addition, effects on memory and other cognitive functions should be estimated both immediately after intake as well as in the morning after.

Therapeutic effects should be demonstrated both in the natural setting as well as in sleep laboratory studies. Although sleep laboratory studies provide opportunity for various types of physiological measures before, during and following sleep, these studies have a limited generalizability due to the artificial setting and the selected type of patient population that typically get recruited into these studies.

The aim of treatment should be the improvement of subjective parameters of disturbed sleep. Improvement should be demonstrated on all elements included in the diagnosis of insomnia, namely: sleep-latency, -continuity, -duration, and daytime functioning. Improvement in daytime functioning can be demonstrated by improved mood and improved cognitive functioning such as perceptual speed, attention, concentration, and memory. At the same time, these parameters should be evaluated as potential hang over effects.

Comparison with placebo as well as with a standard product in parallel group design is indispensable for confirmatory analysis. For pivotal studies, 2 treatment weeks are considered adequate as currently available products are not recommended for longer use. Crossover study may provide supportive evidence for efficacy but are not recommended as pivotal studies.

For the safety assessment, dependence potential, development of tolerance, and discontinuation and rebound phenomena should be evaluated in a placebo discontinuation phase at the end of each study and particularly after studies of longer duration. Moreover, since sleep disorders tend to be chronic, long-term studies (at least 6 month) evaluating the maintenance of effect and long term safety are considered necessary.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The clinical pharmacokinetic program consisted of single and multiple dose-escalation studies (0.3-64 mg), a mass-balance study with labelled ramelteon (ADME study), food-interaction studies and 20 different interaction studies in healthy volunteers. Absolute bioavailability was studied in healthy volunteers using an i.v. solution. A study was performed in renal and hepatic patients. The influence of intrinsic factors like age (elderly), gender and ethnicity was studied. No population PK studies were performed.
Furthermore, PK data were sampled in PD studies on QTc prolongation. Several *in-vitro* PK studies were performed to investigate absorption through tissues, plasma protein binding properties, red blood cell partition and metabolism and interactions of ramelteon and its major metabolite M2.

- Absorption

Bioavailability
In-vitro, permeability and P-gp affinity of C^{14} labelled-ramelteon was tested in a monolayer Caco-2 cells model (Study M-11-00750).^{3}H-digoxin (a control for P-gp substrate) and DL-^{3}H-proponalol (a control for high permeability) were applied as active controls. Quinidine 100µmol/L was applied as P-gp inhibitor. The result of this experiment was that ramelteon was highly permeable, and that the transport was not influenced by P-gp inhibition.

In-vivo, **absolute bioavailability** was investigated comparing ramelteon plasma exposure after intravenous infusion of 2 mg ramelteon (1 mg/mL solution) for 5 min and after a single oral dose of 16 mg, in 20 healthy male volunteers (Study EC003). Absolute bioavailability of the parent drug, calculated by the LS mean of dose-adjusted AUC ratio, was very low, 1.8% (range 0.5-12%). Dose normalised metabolite concentrations (i.e. M2 and M4) were similar after iv or oral administration.
Tmax is estimated to be approximately 0.75 hour (range 0.5-1.5) for parent drug ramelteon and for M2, in fasted condition. Based on this, it would be recommended to take ramelteon 30 minutes before going to sleep.

Since the **M2 metabolite** may account for part of the efficacy/safety (see further in the text, *Metabolites*), the CHMP requested the applicant to perform a PK-PD analysis to assess the clinical impact of changes in M2 exposure. The Applicant did not provide the requested information, as M2 has not been given as a separate drug, this may not be feasible.
Information regarding the intrinsic activity of M2 is relevant for interpretation of variability of plasma levels of M2, caused drug-drug (D-D) interactions or declined metabolic rate.
The Applicant submitted an analysis to what extent the sum of ramelteon + metabolite would be influenced by intrinsic and extrinsic factors influencing pharmacokinetics.
In general, the total sum of active moieties was less sensitive to extrinsic factors such as D-D interactions, and intrinsic factors such as renal or hepatic dysfunction.
Though a study on the PD activity of M2 independently from the parent drug would have been preferred (the contribution of M2 to the total clinical effect is still not clear), it is reassuring that the sum of active moieties is less sensitive to factors causing variability in PK. This finding makes the issue of contribution of M2 less relevant.

Influence of food
Food effect was investigated in three single, cross-over food interaction studies (CPH001, CPH006 & TL004). In study TL004 (performed in the US), a high fat meal was administered. AUC of ramelteon increased with approximately 30% after a meal, but Cmax declined. For M2, Cmax increased with

approximately 30%, but overall the AUC remained stable. Food intake prolonged the tmax from 0.75 hr to 1.5 hr.
In study CPH001, a Japanese study using 8 mg dose, food had a milder effect (but in the similar direction as in Study TL004); AUC of ramelteon increased with approximately 16%, Cmax decreased with 47% and tmax was delayed with 20 min.

- Distribution

Volume of distribution:
The Volume of distribution (Vd) of ramelteon is estimated to be 73.6 L after intravenous administration. As M2 has not been administered as a drug, Vd of M2 could not be estimated.

Protein-binding and partition to erythrocytes: parent drug
Red blood cell distribution was determined using the hematocrit method, and protein binding was determined by ultrafiltration.

In *in-vitro* Study M-11-00049.001A, red blood cell distribution and protein binding in human biomaterials were determined using [^{14}C]ramelteon 0.01, 0.1, and 1 μg/mL added to human blood and serum, and 4% human serum albumin; Ramelteon was distributed into red blood cells for ±25% at all tested concentration levels. Similar results were observed in Study M-11-00905 in human blood. The protein-binding varied between 81.1-83.3% in human serum, and 68.8-71.9% in 4% human serum albumin.

In *in-vitro* Study M-11-00906, [^{14}C]ramelteon added to 0.05% α_1-acid glycoprotein and 4% human serum albumin + 0.05% α_1-acid glycoprotein mixture at concentrations of 0.01, 0.1, and 1 μg/mL. The protein-binding results were 56.3-62.9% in α_1-acid glycoprotein, and 83.3-84.6% in the mixture of human serum albumin + α_1-acid glycoprotein.

Protein-binding: M2
In in-vitro Study M-11-00536, M2 was added to human serum at concentrations of 0.01, 0.1, and 1 μg/mL. The protein-binding results were 79.1%, 77.1%, and 76.5%, respectively.

Ex-vivo protein binding in patients with hepatic or renal impairment.
The percentage of protein binding of both ramelteon and M2 was similar in samples from healthy subjects and subjects with renal or hepatic impairment, despite hypoalbuminemia in some patients. Moreover, the ex-vivo data were similar to binding percentages found.

- Elimination

Excretion
In mass balance study EC004, a single oral dose of 16 mg ^{14}C-labelled ramelteon (3.16 MBq) was administered to 6 healthy male volunteers. Blood, faeces and urine was sampled up to 8 days (196 hrs) post-dose.

Mass balance study: Total radioactivity:
On average 88% of the total radioactivity was recovered. The principal route of excretion of total radioactivity was in urine (84%). Faecal recovery of radioactivity accounted for an additional 4% of the dose. Renal elimination of total radioactivity was rapid and occurred within the first 24 hours. Elimination was essentially complete by 96 hours postdose.

Mass balance study: active compounds
About 50-70% of total radioactivity could be explained by ramelteon and its metabolites.

In first instance, the MAH had only analysed the samples for M1-M4, under the assumption that these are the main metabolites. However, except for M2, the unconjugated metabolites contributed to minor extent to total radioactivity.

In a later phase glucuronides-metabolites were measured in total urine, and in serum samples taken 20 minutes and 4 hrs after dosing. In serum, M2 accounted for approximately 30% of serum radioactivity, and glucuronide-conjugates for another 20-30% at different time-points.
Ramelteon is mainly excreted as glucuronides conjugates (33%) and oxidised metabolite U8 (30%) into urine. Only 4.6% of the dose was excreted into urine as unconjugated metabolite (sum M1-M4). Unchanged parent drug was recovered in faeces and urine in minimal quantities (<1% and 0.001%, respectively).

The CHMP requested the applicant to clarify the configuration of major urinary metabolite U8 and whether it found in the serum. The applicant explained that U8 is the glucuronide conjugate of M8, the di-hydroxy-metabolite of ramelteon (and the hydroxy-metabolite of M8), and it is not recovered in the serum
Furthermore, only part of the recovered radioactivity (about 58% in urine and 65-70% in serum) had been fully characterised. As the radio label was conjugated to a propionamide moiety, the applicant was requested to discuss whether metabolites without the radioactive moiety are biologically active.
It was shown that metabolites of the propionamide moiety without the labelled ethyl group are expected to form a minor percentage of the metabolites, and therefore it is not relevant whether the propionamide part is biologically active.

Metabolism
Half-life
Half-life of ramelteon was estimated as 0.75-2 hours in several studies, and is dose independent. Half-life of M2 is estimated in range of 2-3 hours
Clearance after short-time iv infusion was estimated as 55.5 L/hr. Cl/F after oral administration was estimated in a range of 2000-6000 L/hr.

Metabolites
The main active metabolite M2 is the hydroxy-metabolite of the propionamide moiety of ramelteon. M2 has approximately one tenth and one fifth the binding affinity of the parent molecule for the human MT_1 and MT_2 receptors, respectively, and is 17-25-fold less potent than ramelteon *in vitro* functional assays. Although the potency of M2 at MT1 and MT2 receptors is lower than the parent drug, M2 circulates at higher concentrations than the parent producing 20-100 fold greater mean systemic exposure when compared to ramelteon. M2 has weak affinity for the serotonin 5-HT2B receptor.

Minor inactive metabolite M3 is an oxidised metabolite. Minor metabolite M4 might be derived by further oxidation of M2 and/or M3.

Involved CYP enzymes
CYP isozymes involved in the biotransformation of ramelteon in humans were determined using human B-lymphoblastoid–derived microsomes expressing CYP isozymes (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) incubated with ramelteon at concentrations of 50 µmol/L. A correlation study was also conducted using human hepatic microsomes from individual donors.
CYP1A1, CYP1A2, CYP2C9, CYP2D6, and CYP3A4 were identified as the CYP isozymes involved in the biotransformation of ramelteon *in-vitro*. *In-vitro* correlation studies between metabolic activity of ramelteon and that for CYP isoform specific substrate using individual liver microsomes (n=15) indicate that to large extent CYP1A2, and to minor extent CYP2C9 and CYP3A4 are involved in the hepatic metabolism of ramelteon. M2 is mainly metabolised by CYP3A4 and 2C9.

Inter-conversion
Ramelteon is produced as an S-enantiomer, as it is the most active form.
In-vitro, hydroxylation to M2 by CYP1A2 is stereoselective, resulting predominantly in a single enantiomer, which exists as a 2*S*,8*S*-diastereomer, i.e. a second chiral centre in the propionamide moiety (M-11-00512, M-11-00327). *Ex-vivo*, all M2 recovered in serum had the 2S,8S configuration after a single dose of 2 mg (from clinical Study CPH001, report M-11-00368).
At the time of the application, a study to assess the interconversion to the *R* enantiomer was ongoing.

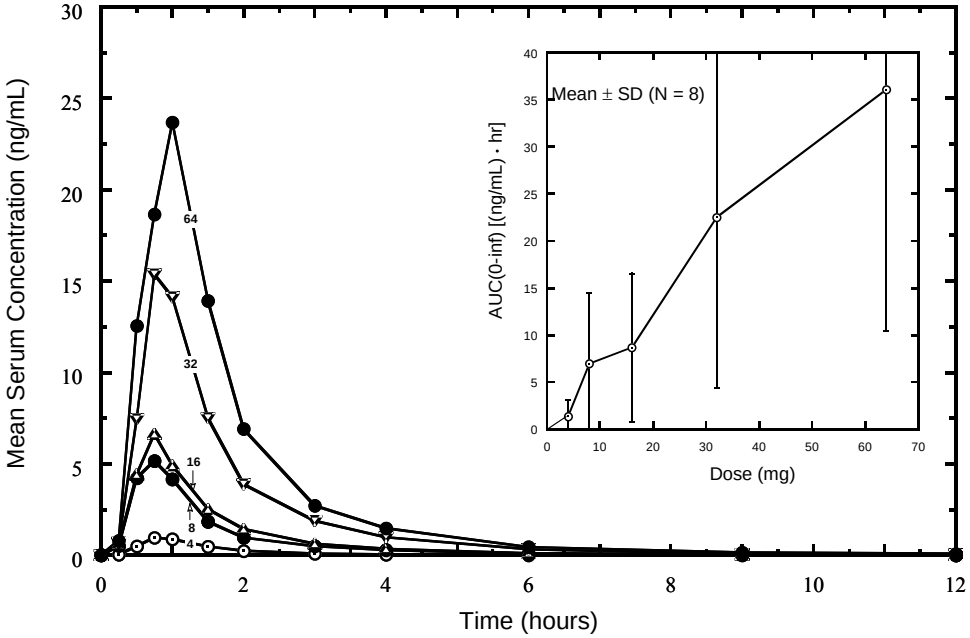
Pharmacokinetics of metabolites
The major metabolites of ramelteon are glucuronide conjugates of single (M9) or double hydrolyse-metabolites, formed from M9 and M2, respectively.
Furthermore, the applicant during the assessment of the application clarified that M2 is not directly conjugated to glucuronides, but that glucuronidation only occurs after hydroxylation of M2 into M8. As M2, a biological active metabolite, is not only conjugated but also hydroxylated, indicating a significant change in molecule structure, it seems less likely that this conjugate metabolite would have similar receptor affinity and thus biological activity as M2.

Consequences of possible genetic polymorphism
As no genotyping was performed, no firm conclusions could be drawn regarding influence of polymorphism regarding ramelteon metabolism. As no significant differences in plasma exposure of ramelteon and M2 between Asians and Caucasians were observed and considering the broad therapeutic window of this drug, the CHMP considered to be no need to further explore the influence of genetic variability.

- Dose proportionality and time dependencies

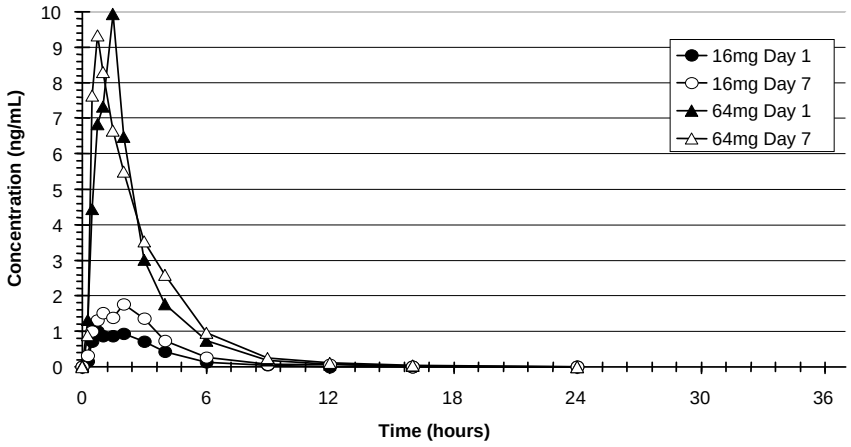
Dose proportionality
Dose-linearity was tested in 40 healthy volunteers, males and females from US (Study PNFP001). The subjects received a single dose of either 4, 8, 16, 32, and 64 mg ramelteon, separated by two weeks. According to the Applicant, exposure to ramelteon and its major active metabolite M2 is linear related to dose (see figure II.1.6.1below). T½ remained stable over the different dosages, indicating linear kinetics.
The mean AUC levels after the 8 mg dose seems out of line, but this may be due to small samples size and high variability of ramelteon.

Figure II.1.6.1 Dose Proportionality of Ramelteon at 4, 8, 16, 32, and 64 mg



Time dependency
Study EC002 was a European ascending dose study to study multiple dose PK in 23 healthy volunteers of both genders. Either 16 or 64 mg ramelteon was administered once daily for 7 days, with a wash-out of 15 days between the two dosing periods. Doses were taken 3 hours after an evening meal, and samples where taken at night.
The mean ramelteon AUC levels increased with 76% after daily dosing of 16 mg for a week, but remained practically stable with the 64 mg regimen (see Figure II.1.6.2 below).

Figure II.1.6.2 AUC after single and multiples dosing of 16 and 64 mg.



The mean exposure at the 16 mg dose was higher after multiple doses compared with the first dose. This phenomenon is unlikely to result from either time-dependent pharmacokinetics or accumulation as the phenomenon was not observed in the higher dose group (64 mg). Rather, the high variability in the disposition kinetics of ramelteon and high inter-occasion variability is likely to explain the apparent accumulation.

- Special populations

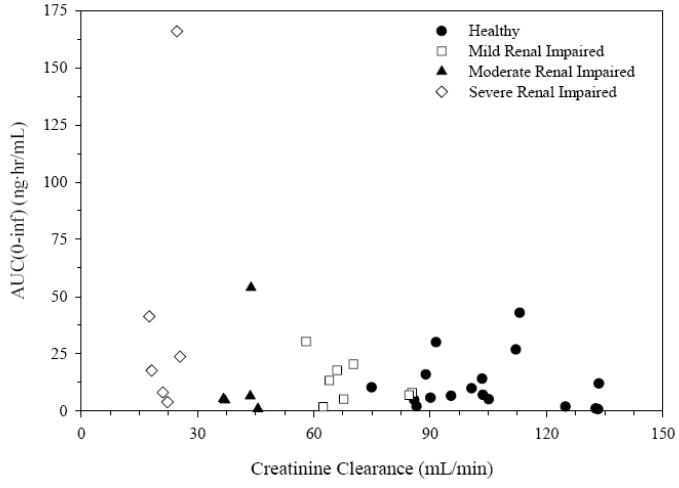
Impaired renal function

In Study TL030 on renal impairment, 50 subjects enrolled and 49 subjects completed the study. Subjects with mild, moderate and severe renal impairment and subjects who required chronic haemodialysis were matched with healthy subjects.

Subjects received a single dose of ramelteon 16 mg on Day 1 followed by a 2-day washout on Days 2 and 3. Subjects received ramelteon 16 mg QD on Days 4 through 8. All doses were administered in the morning under fasting conditions.

Exposure to ramelteon was highly variable, and although extreme values were observed in the severely impaired group, statistical significance was not reached in this small sized study. AUC of M2 was slightly (50%) and statistically significant higher in the group with severe renal impairment. Exposure to ramelteon and non-conjugated metabolites M1-4 was similar at Day 1 and 8.

As shown in the figure below, there was no clear relationship between ramelteon exposure and creatinine clearance.



Impaired hepatic function
Forty-eight subjects (12 subjects with mild hepatic impairment (Child-Pugh A) matched with 12 healthy subjects, and 12 subjects with moderate hepatic impairment (Child-Pugh B) matched with 12 healthy subjects) enrolled and all completed the study. Most patients were suffering from hepatitis C. Subjects received a single dose of ramelteon 16 mg on Day 1 followed by a 2-day washout on Days 2 and 3. In addition, subjects received ramelteon 16 mg QD on Days 4 through 8. All doses were administered in the morning under fasting conditions.

Ramelteon AUC was 6 (90% CI 2-15) times higher in patients with mild hepatic impairment and approximately 10 times higher in patients with moderate hepatic impairment compared to the healthy reference group. M2 AUC values were similar in subjects with mild-moderate hepatic impairment compared to healthy reference population.

There was no apparent correlation between the severity of hepatic impairment and the increase in exposure to ramelteon in subjects with Child Pugh scores between 5 and 8. However, 3 subjects with moderate hepatic impairment, who had Child-Pugh scores of 9, exhibited substantially higher exposures to ramelteon than any of the other subjects in the study.

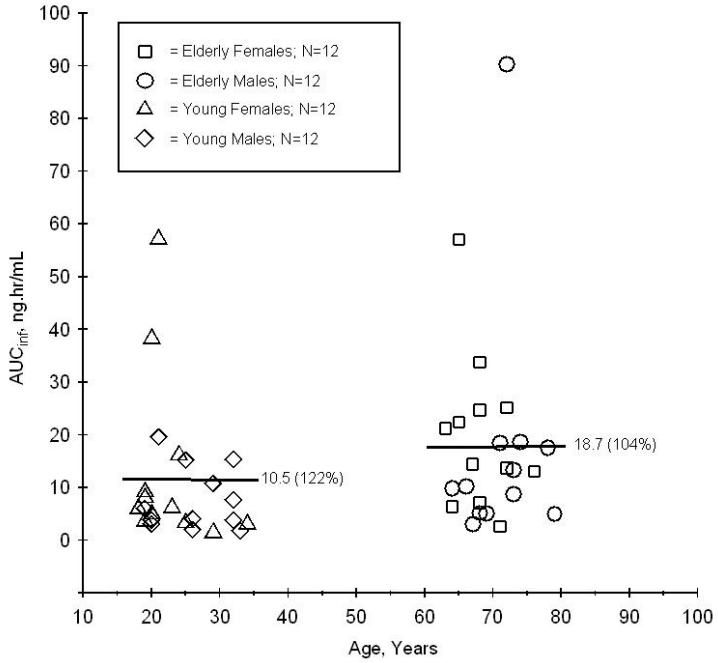
Short-term safety data of this PK study revealed that despite the high exposure, tolerability was rather similar in hepatic patients and healthy subjects.

Gender
The effect of gender on serum exposure was evaluated in data from Study TL003, 24 males and 24 females. There were no statistical significant differences (90% CI ratio AUC: 86-204, 90% CI ratio Cmax: 76-186).

Race
Results from a meta-analysis, conducted to compare PK parameters for both ramelteon and M2 in Caucasian and Japanese men, showed that ethnic differences in CYP1A2 do not produce significant differences in ramelteon metabolism.

Weight
Despite high distribution volume, there was no significant influence of body weight on serum exposure. Weight did not explain the large inter-individual variability in serum exposure. No dose adjustments for high bodyweight are indicated.

Elderly
In a group of 24 elderly subjects aged 63 to 79 years administered a single ramelteon 16 mg dose, the mean Cmax and AUC0-inf values were 11.6 ng/mL (SD, 13.8) and 18.7 ng·hr/mL (SD, 19.4), respectively. The elimination half-life was 2.6 hours (SD, 1.1). Compared with younger adults (aged 18-34), the total exposure (AUC0-inf) and Cmax of ramelteon were 97% and 86% higher, respectively, in elderly subjects (see figure below). The AUC0-inf and Cmax of M2 were increased by 30% and 13%, respectively, in elderly subjects. A similar effect were observed in Japanese elderly subjects (CPH005)



Children
No studies were performed in children

- Pharmacokinetic interaction studies

In vitro
The effect of ramelteon and M2 on the activities of microsomes expressing human CYP isoforms was investigated using specific markers (see table II.1.10.1 below). In high concentrations above 10 µmol/L, a decrease in activity of CYP2C8, CYP2C19 CYP3A4 of 50% was observed. Of note, *in-vivo* Cmax values after an 8 mg dose are 1000 fold lower than the test conditions.

Table II.1.10.1, IC50 Values of Ramelteon and M2 For Human Recombinant CYP Isoforms

	IC50 Value				
	Ramelteon		M2		
CYP	µg/mL	µmol/L	µg/mL	µmol/L	CYP Substrate Marker
CYP1A1	>25.9	>100	>27.5	>100	7-ethoxyresorufin
CYP1A2	>25.9	>100	>27.5	>100	7-ethoxyresorufin
CYP2A6	>25.9	>100	>27.5	>100	coumarin
CYP2B6	>25.9	>100	>27.5	>100	ethoxycoumarin
CYP2C8	2.59-25.9	10-100	>27.5	>100	tolbutamide
CYP2C9	>25.9	>100	>27.5	>100	tolbutamide
CYP2C19	2.59-25.9	10-100	>27.5	>100	(S)-mephenytoin
CYP2D6	>25.9	100	>27.5	>100	bufuralol
CYP2E1	>25.9	>100	>27.5	>100	p-nitrophenol
CYP3A4	2.59-25.9	10-100	>27.5	>100	Testosterone

The *in vitro* cytochrome P450 induction potential of ramelteon and M2 was studied in human hepatocytes (Study M-11-00563). Ramelteon induced CYP3A activity in a concentration-dependent manner up to 30 µmol/L, but the induction activity of ramelteon was much weaker compared to that of rifampicin, a known CYP inducer. M2 up to 30 µmol/L did not induce CYP3A.

In vivo

The influence of typical CYP-inhibitors on ramelteon/M2 exposure

The effect of CYP1A2 inhibitors fluvoxamine, CYP3A4 inhibitor ketoconazole, CYP2C9 inhibitor fluconazole and CYP2D6 inhibitor fluoxetine was studied in-vivo. As expected based on *in-vitro* studies, CYP1A2 inhibitor fluvoxamine blocked the first-pass effect and had a huge increasing effect on ramelteon exposure (AUC increased more than 190 fold), but an insignificant effect on M2 levels. The inhibitory effect declined after repeated use of fluvoxamine for 7 days compared to 4 days. Tmax increased significantly after boosting with fluvoxamine from 1.3 to 4 hours.

CYP3A4 inhibitor ketoconazole and CYP2C9 inhibitor fluconazole had moderate effect on ramelteon levels (1.5-2 times increment), and a somewhat stronger effect on M2 (2-3 times increment)

CYP2D6 inhibitor Fluoxetine caused mild increment of ramelteon and M2 level of 50%.

The influence of CYP inducers on ramelteon/M2 levels:

Rifampicin acted as a strong unspecific CYP inducer leading to 80% lower levels of ramelteon/M2, at high doses ramelteon of 32 mg. Omeprazole had a mild inducing effect on CYP1A2, leading to 30% lower ramelteon levels. However, M2 levels slightly increased, indicating that omeprazole might not induce other CYP enzymes.

The influence of other drugs/substances on ramelteon/M2 exposure

When ramelteon was co-administered with another CYP1A2 substrate theophylline, no significant competitive inhibition was observed, as the theophylline levels remained constant, and ramelteon/M2 increased slightly with 40%.

Remarkably, **alcohol** has a mild increasing effect on ramelteon AUC, but not on M2 (ramelteon AUC levels increased with 47% (90% CI 4-106%). The mechanism underlying this interaction is not understood.

Co-administration of anticonvulsant gabapentin, a substance that is renally cleared, 400 mg TID for 9 days had no significant influence on ramelteon PK (changes less than 30%).

Donepezil, a reversible acetylcholine-esterase inhibitor, caused doubling of the ramelteon levels, but no change in M2.

Tobacco smoke is a well-known CYP1A2 inducer which would very likely lower the ramelteon levels. Since induction of the metabolism of ramelteon causes enhanced levels of the metabolite M2, and as this metabolite is biological active, this may compensate lower levels of the parent drug.

PK interactions with antidepressants

The influence of antidepressants sertraline, venlafaxine and escitalopram on a PK of ramelteon was tested. These antidepressants had no significant effect on ramelteon /M2 exposure. Tricyclic antidepressant doxepin caused a mild increment of ramelteon level of 65% (90% CI 27-115), but M2 remained unchanged.

Vice versa, multiple dose of ramelteon had no significant effect on fluvoxamine, sertraline, venlafaxine, escitalopram and doxepin.

The effect of Ramelteon on other drugs:

In-vivo, ramelteon had no influence on metabolism of CYP2C19 substrate omeprazole, CYP2D6 substrate dextromethorphan and its metabolites, theophylline (CYP1A2 substrate), midazolam (CYP3A4 substrate), nor R- and S-warfarin (substrate for CYP1A2 and CYP2C9, respectively). Neither did ramelteon (16 mg, multiple dose) influence P-gp substrate digoxin. Ramelteon had no influence on gabapentin (renally cleared) or donepezil.

As no significant changes of T4/TSH levels were observed in a clinical safety study (TL032) where ramelteon 16mg was daily administered for 6 months, shared glucuronidation pathways in the metabolic clearance of ramelteon and metabolites and thyroxine seem not very likely to occur.

Pharmacodynamics

Effects on sleep structure, next morning memory, concentration, alertness, reaction time, sedation, mood, and psychomotor function were assessed in different studies with different dose ranges in younger and older adults. In addition, abuse liability was assessed in 2 studies with ramelteon, placebo, and triazolam as an active comparator.

- Mechanism of action

The sleep-wake cycle is influenced by the circadian rhythm, which is in turn controlled by the suprachiasmatic nucleus (SCN). The SCN emits alerting signals, which are attenuated by melatonin that is produced in response to darkness. Binding of melatonin to MT1 and MT2 receptors in the SCN inhibits firing of specific neurons, and this is thought to attenuate the alerting signal thereby allowing the homeostatic mechanism to express itself and promote sleep.
The claimed mechanism of action of ramelteon propionamide, (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl], is through its affinity and selectivity for human melatonin MT1 or MT2 receptors. This affinity was demonstrated in in-vitro models. In addition, ramelteon is claimed to have full agonist activity relative to melatonin in cells expressing human MT1 or MT2 receptors.
Ramelteon and its active metabolite, M2, are claimed to have negligible affinity (Ki greater than 10 μM) for the GABA-A receptor complex, as well as for receptors that bind dopamine, serotonin, acetylcholine, glutamate, noradrenaline, and various neuropeptides, cytokines, and opiates. Therefore, ramelteon is not expected to produce effects associated with the use of hypnotics, including sedation, anxiolysis, muscle relaxation, and amnesia.

- Primary pharmacology

Sleep architecture
Possible effects of ramelteon on sleep architecture were measured in three laboratory studies using polysomnography (PSG), and focusing on three parameters: latency to rapid eye movement (REM) sleep, percentage of total sleep time spent in REM sleep, and percentage of total sleep time spent in non-rapid eye movement (NREM) Stages 1, 2, and 3/4. The study design and results are presented in table 1 below.

Table 1 (clinical). Effects on sleep architecture in three laboratory studies

		Ramelteon			
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**
TL005; 5-period crossover study, 2 nights, adults with insomnia ; n=103					
Latency to REM (min)	79.3±40.03	80.1±39.14	75.2±29.12	77.4±35.40	79.0±41.39
% time in REM	20.9±5.27	20.2±5.71	21.0±5.54	20.5±5.18	21.1±5.98
% time in NREM Stage 1	11.0±6.04	11.4±5.67	11.4±5.12	11.7±5.72	11.9±6.59
% time in NREM Stage 2	53.0±10.49	54.7±10.65	54.3±10.65	54.4±10.70	54.1±10.82
% time in NREM Stage 3/4	15.0±10.44	13.7±10.74*	13.2±9.90*	13.4±10.56*	12.9±10.19*
TL017; 3-period crossover study, 2 nights, elderly subjects with insomnia; n=100					
Latency to REM (min)	72.8±31.85	68.5±31.67	66.9±28.76	NA	NA
% time in REM	20.0±5.48	20.1±5.32	20.1±5.25	NA	NA
% time in NREM Stage 1	12.8±5.49	13.6±6.17*	14.0±6.30*	NA	NA
% time in NREM Stage 2	55.8±9.77	56.8±9.29	57.7±9.04*	NA	NA
% time in NREM Stage 3/4	11.5±10.95	9.5±9.72*	8.3±9.70*	NA	NA
TL021; parallel-group study, 35 nights, adults with insomnia					
N	131	NA	138	135	NA
Latency to REM (min)	79.5±41.20	NA	74.8±34.77	74.0±29.43	NA
% time in REM	20.8±5.94	NA	21.9±5.18	21.1±5.30	NA
% time in NREM Stage 1	9.5±5.03	NA	10.2±4.46	10.2±5.49	NA
% time in NREM Stage 2	60.1±8.28	NA	59.7±7.35	60.6±8.29	NA
% time in NREM Stage 3/4	9.6±8.21	NA	8.2±7.05	8.1±7.34	NA

NA= not applicable. *P<0.05 from Dunnett t-test from analysis of (co)variance. All values are mean±SD

As the table indicates, latency to REM while under ramelteon treatment is somewhat shorter compared to placebo (up to a maximum of 6 minutes less). However, these small reductions do not reach statistical significance. In addition, it is not clear if the reduction in latency to REM is a function of the reduction of latency to sleep onset (the primary efficacy outcome). Percent time in NREM sleep under ramelteon treatment is somewhat higher for stage 1 at the expense of stage 3 (deep sleep). Some of these differences are statistically significant (in study TL017).

Although, these differences do not seem to have clinical relevance, the association of ramelteon treatment with shorter rather than longer duration in deep sleep is unexpected. Altogether, the impact on sleep architecture is minimal.

- Secondary pharmacology

Balance
Since balance is known to be negatively affected by currently available sleep medications (BZRA) and balance is related to the risk of falls, it was decided to investigate the effect of ramelteon on balance. Three clinical studies examined the effect of ramelteon on balance compared to that of an active control (zopiclone or zolpidem) and placebo. In these studies subjects were awakened in the middle of the night and their balance evaluated.
In all three studies, the results for ramelteon-treated subjects were similar to those seen in subjects receiving placebo while both comparators appeared to have statistical significant negative impact on measures of balance performance.

Abuse Liability
In two studies that examined abuse liability in humans, ramelteon was administered in a randomized sequence with placebo and triazolam. Abuse liability was assessed using the Next Day Questionnaire, Addiction Center Research Inventory, Drug Effect Questionnaire, Subjective Effects Questionnaire, Observer Rated Questionnaire, and Pharmacologic Class Questionnaire.
Triazolam showed dose-related responses on all subject- and observer-rated measures, indicative of abuse liability. On the contrary, for all of the above assessments, subjects did not differentiate ramelteon from placebo.

Withdrawal and Rebound
Post-treatment *withdrawal effects* were evaluated using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) in four of the efficacy trials (EC302, TL021, TL025 and TL020). The BWSQ is a self-report questionnaire designed to record the symptoms experienced during withdrawal from benzodiazepines in pharmacologically dependent patients. The questionnaire is a reliable instrument with acceptable evidence regarding validity. It was completed during the single-blind run-out period when subjects in these studies were switched from active treatment to placebo and compared to the final BWSQ value collected while on treatment. Subjects were asked to recall 20 symptoms experienced in the last 24 hours. Each symptom was evaluated on a 3-point scale. The total BWSQ score is the sum of the 20 individual symptom scores.
No evidence of withdrawal symptoms was observed up to 7 days after discontinuation of ramelteon. In Study TL021, a statistically significant reduction was seen in the BSWQ score for the ramelteon 16 mg group compared to placebo on the first post-treatment day, but the direction of the change does not support the presence of a withdrawal effect.

Possible *rebound insomnia* was evaluated in the same four studies as those analysed for withdrawal. Subjects' sleep latency in the placebo run-out period was compared to the single blind placebo run-in period. In two studies latency was estimated from (objective) PSG measures while in the remaining two studies, subjective measures were assessed: the average of the first 7 nights of the single-blind placebo run in period compared to each day following discontinuation of treatment during the single-blind placebo run-out period.
No changes in sleep latency suggestive of rebound insomnia were seen.

The lack of active control to validate the sensitivity of these studies to detect withdrawal and rebound limits the interpretation of the results. Without an active control it is difficult to claim advantage of ramelteon compared to e.g. benzodiazepines. In addition, the questionnaire that was used in the studies was designed to assess withdrawal symptoms typical for benzodiazepine but does not address potential withdrawal symptoms from ramelteon, which are not necessarily identical to the benzodiazepines withdrawal symptoms. Based on the available information it would be difficult to defend a claim of an advantage in terms of safety.
Furthermore, the absence of withdrawal/rebound phenomena may also be due to a lack of a pharmacodynamic effect of ramelteon.

Ability to Drive or Operate Machinery
Study EC103 was specifically designed to assess the effects of ramelteon, zopiclone, and placebo on driving ability 8.5 hours after bedtime administration. Both the ramelteon and zopiclone treatments demonstrated a statistically significant increase compared with placebo in mean standard deviation of lateral position (SDLP) scores P<0.001). SDLP was increased relative to placebo by 2.2 cm and 2.9 cm for ramelteon and zopiclone, respectively.

Analyses on the effect of alcohol on driving performance have shown that an increase in SDLP of 2.4 cm is equivalent to a blood alcohol content of 0.05%, the legal limit for driving in many countries. Following treatment with ramelteon, the mean SDLP was below 2.4 cm. Following treatment with the active comparator, the mean SDLP increase was above 2.4 cm.
The argumentation above from the applicant was considered insufficient by the CHMP. In fact, the concern about motor vehicle accidents raised later (see section on serious adverse events and deaths) was reinforced by the findings regarding deviation and other next-morning effects.

Additional next-morning effects showed both the ramelteon and zopiclone treatments were associated with statistically significantly worse results compared to placebo for the following parameters:

- reaction times
- divided attention test
- motor control test
- delayed word recall test

The percentage errors for a memory test were also higher compared to placebo, although the differences were not statistically significant.
The company argued that the evidence of impairment seen in Study EC103 were in a small number of subjects and may have resulted from the midnight waking of subjects required by the study design.

Cognition, perception, and emotions
Next morning effect on cognition, perception, sedation and psychomotor performance as well as sleep measurements were assessed in a 2-period crossover study of 7-day treatment with ramelteon 16 or 64 mg and placebo nightly. Healthy volunteers (n=20) were included in this study.
There were no statistically significant findings for next morning measures of sedation, speed of information processing, memory, sleep architecture or psychomotor performance. However, there was a trend for both ramelteon doses to increase sedation and reaction time the next morning. There was also a non-significant trend for reduction in anxiety the next morning. When the two ramelteon groups were pooled together this difference became significant.
In another 2-period cross-over study of 7-day treatment with ramelteon 16 mg with 48 healthy volunteers of whom 24 (12 males and 12 females) were 18-35 years old and 24 (12 males and 12 females) 60+, no clinical meaningful difference from baseline or between older and younger subjects were observed for any of the PD parameters.
A food effect study showed no statistical significant difference between fed and fasted subjects in cognitive parameters. However, sedation was greater under fasted compared to the fed condition. There was no gender difference.

Critical Flicker fusion is defined as the frequency at which an intermittent light stimulus appears to be completely steady to the observer. As the flicker fusion threshold also is higher for a fatigued observer it used as a measure of sedation.
Without an active control, it was difficult to interpret the results of these studies. Moreover, reactivity of healthy volunteers may be different from that of patients with insomnia.

Pharmacodynamic interactions with other medicinal products or substances
Interaction with ethanol was investigated in several studies where 32 mg ramelteon was administered with 0.6 g/kg ethanol concomitantly. The results showed no additive effects on psychomotor function, memory, alertness, immediate and delayed recall. However, the results demonstrated an additive interaction on reaction time and alertness. It is therefore concluded by the MAH that patients should be advised to exercise caution if they consume alcohol in combination with ramelteon.

Clinical efficacy

Efficacy of ramelteon in insomnia was initially investigated in 11 clinical studies, 10 short-term and one long-term. All were randomized, multicenter, double-blind, placebo-controlled, dose-response studies. An overview of all clinical studies is presented in table 2. As the table indicates the studies are grouped into four categories, including:

- 3 natural setting studies (TL020, TL025, CCT002), which are considered the pivotal trials in this dossier. All three were short-term studies (up to 5 weeks).

The remaining eight studies were conducted in laboratory settings, including:

- 3 parallel group studies (TL021, EC301 EC302) of which the first 2 were short-term studies and the latter a 6-month study. EC301 was primarily a safety study which includes evaluation of efficacy as well and included an active comparator arm (zopiclone).
- 3 crossover studies (TL005, TL017, and CCT001)
- 2 healthy volunteers studies (PNFP002 and TL023) that were performed in order to examine a transient insomnia model. These studies had a crossover design.

During the assessment of the MAA, the applicant has submitted additional data including:

- final results for the long-term study (EC302) for which only preliminary results were available at the time of the original submission
- a new phase 2 parallel group study (TL055) which was designed to assess the efficacy of Ramelteon combination with Gabapentin and included with 2 nights in the laboratory with PSG measures and 5 nights at home with subjective sleep measures.

The primary efficacy parameter in all studies was latency time to persistent sleep (Sleep Latency or SL). In the natural setting studies, this parameter was subjectively assessed (sSL) via sleep diaries; in the sleep laboratory studies, it was objectively measured by polysomnography (PSG). Additional methods for assessing sleep latency were used in some studies, including post sleep questionnaires (PSQ) and an interactive voice recording system (IVRS). Both these methods assess the subjective experience of sleep latency but in a more structured way than sleep diaries.

Since insomnia is diagnosed and treated based on subjective complaints about sleep problems in the natural setting, and due to the limited generalisability of effects seen in the laboratory, the subjectively assessed sleep latency in the natural setting studies (the pivotal studies) are considered the most relevant for demonstrating efficacy. The sleep laboratory studies can examine the pharmacological effect on sleep and are considered supportive.

The weakness of sleep latency as an outcome variable is its' sole reliance on only one aspect of sleep, thereby neglecting additional aspects, i.e. sleep duration, number of awakenings and next day functioning. For a claim of insomnia, effect should be demonstrated on all components of sleep, not just one. Some of these other aspects of sleep were assessed as secondary outcome in the studies. However, next day functioning was not even assessed in any of the studies.

Only one study (EC301) had an active control arm zopiclone. The lack of an active control arm in all other studies limits the interpretations of the results with respect to efficacy and safety (see below).

Table 2: Design of Ramelteon studies

Study ID	No. of centres/ locations	Design/ treatment duration	Dose in mg	Setting	Ns entered/completed	Population/ mean age (SD)	Dx Incl. criteria	Primary Endpoint
STUDIES IN NATURAL SETTING								
TL020	79/ US	Parallel / 35 nights	8, 16	Outpatient	Plc: 287/242 8mg: 277/232 16m: 284/238	Adult 18-64 44 (12)	DSM-IV Chronic insomnia >3month	sSL mean first week
TL025	136/ US & Canada	Parallel/ 35 nights	4, 8	Outpatient	Plc: 274/228 4mg: 281/234 8m: 274/239	Elderly 65+ 72 (6)	DSM-IV Chronic insomnia >3month	sSL mean first week
CCT002 ([a]	141/Japan	Parallel / 28 nights	4, 8, 16	Outpatient	Plc: 380/368 4mg:372/355 8mg: 378/360	Adults &Elderly 20-85	DSM-IV Chronic insomnia >3month	sSL mean first week
SLEEP LABORATORY STUDIES								
TL021	29/ US	Parallel/ 35 nights	8, 16	Sleep laboratory and outpatient	Plc: 131/119 8mg: 139/124 16m: 135/128	Adult 18-64 39 (12)	DSM-IV Chronic insomnia >3month	PSG LPS Mean 1st 2 nights
EC301 (safety study)	36/ EU & Australia	Parallel/ Active comparator/ 28 nights	8mg Ramelteon; 7.5mg Zopiclone	Sleep laboratory and outpatient	Plc: 94/89 ram: 88/80 zop: 93/80	Adult 18-64 42 (13)	DSM-IV Chronic insomnia >3month	PSG LPS Mean 1st 2 nights[b]
EC302	46/ EU, US, Australia & Russia	Parallel/ 6 months	8	Sleep laboratory and outpatient	Plc: 224/176 8m: 227/159	Adult & elderly 18+ 46 (15)	DSM-IV Chronic insomnia >3month	PSG LPS at month 3&6
Sleep laboratory studies: crossover designs								
TL005	13/ US	Crossover /2 nights per dose	4,8,16,32	Sleep laboratory	107 / 103	Adult 18-64 38 (12)	DSM-IV Chronic insomnia >3month	PSG LPS 2 nights
TL017	17/ US	Crossover /2 nights per dose	4, 8	Sleep laboratory	100/67	Elderly 65+ 71 (5)	DSM-IV Chronic insomnia >3month	PSG LPS 2 nights
CCT001	23/Japan	Crossover /2 nights per dose	4,8,16,32	Sleep laboratory	65/60	Adult 20-65 43 (14)	DSM-IV Chronic insomnia >3month	PSG LPS 2 nights
Sleep laboratory studies: healthy volunteers								
PNFP002	14/ US	Parallel/ 1 night	16, 64	Sleep laboratory	Plc: 123/123 16m: 126/126 64mg: 126/126	Adult 35-60 44	Healthy volunteer	PSG LPS 1 night
TL023	15/ US	Parallel/ 1 night	8, 16	Sleep laboratory	Plc: 97/96 16m: 98/98 64mg: 94/94	Adult 18-64 29 (9)	Healthy volunteer	PSG LPS 1 night

- **Study Participants**

Subjects were recruited mostly by advertisement, although some subjects in some studies were recruited by the investigators from their own patient population.

All studies, except the two healthy volunteer studies, included subjects who met diagnostic criteria for insomnia according to DSM-IV-TR. To meet diagnostic criteria for insomnia, DSM-IV-TR required the symptoms to be of a minimum duration of 1 month. The ramelteon insomnia studies required a minimum duration of insomnia symptoms of 3-month and labelled this as chronic insomnia.
Additional inclusion/exclusion criteria were:

Inclusion criteria
To pass the first screening phase subjects had to meet the following conditions (based on subjective reporting):

- subjective sleep latency (sSL) >= 30 minutes,
- subjective total sleep time (sTST) <= 6.5 hours per night
- daytime complaints associated with disturbed sleep
- Subjects with underlying conditions that are characteristics of secondary insomnia were excluded.

A second phase screening included single blind placebo run-in period in which subjective (sleep diary) or objective (PSG) measures of sleep latency (LPS), total sleep time (TST), and number and duration of waking up during the night were ascertained. In the natural setting studies these parameters were averaged over 7 nights of single blind placebo while in the laboratory studies an average over two nights was taken. To be included subjects had to meet the following criteria:

- mean sleep latency (SL) > 20 minutes
- mean wake time > 60 minutes

Exclusion criteria
Subjects were excluded if they had any of the following:

- a history of psychiatric disorders, significant clinical illness within the last 30 days
- were smoking.
- had used any CNS medication (or other drugs or supplements known to affect sleep/wake function) within 1 week (or 5 T1/2s of the drug, whichever was longer) prior to the first day of single-blind study medication.

The two healthy volunteer studies enrolled healthy subjects with normal sleep history. These studies were designed to assess the effect of ramelteon on transient insomnia through use of the first-night-effect model. This model utilizes subjects who are naïve to the sleep laboratory, in order that they may develop transient insomnia when trying to sleep within the unfamiliar environment of the sleep laboratory.

Treatments
Subjects were instructed to self-administer study drug 30 minutes prior to bedtime. In sleep laboratory studies, drug was administered 30 minutes prior to bedtime.

Objectives
The purpose of the studies was to demonstrate efficacy and safety of ramelteon in the treatment of primary insomnia.

Outcomes/endpoints
The primary outcome variable in all studies was the average latency to persistent sleep (LPS) during the first week of treatment (in natural setting studies) or over the first 2 nights of treatment (in sleep laboratory studies) vs. the baseline average (ascertained during placebo run-in). In the three natural setting studies LPS was estimated based on subjective reporting of sleep latency (sSL) derived from sleep diaries. Subjects were instructed to complete the sleep diaries upon awakening in the morning after having slept at home. In the remaining studies, LPS was estimated based on measures from a polysomnograph (PSG) while subjects were spending the night in a sleep laboratory.
PSG is carried out in a sleep laboratory during the night. Sensors, placed on the subjects' body, record various sleep parameters including brain electrical activity, eye and jaw muscle movement, ECG, etc. The information is then stored digitally and allows assessment of e.g. latency time prior to persistent sleep, where persistent sleep is defined as 10 minutes of continuous sleep that followed the pattern: stage 1, 2, and 3/4 non-rapid eye movement sleep (NREM), rapid eye movement (REM) sleep.

In addition to PSG measures, subjective sleep latency was assessed in sleep laboratories by post-sleep questionnaires that were filled out upon awakening.

Secondary outcome variables included: total sleep time (TST), sleep efficiency, wake time after persistent sleep onset (WASO), and number of awakening after onset of persistent sleep (NAW). These parameters of sleep were assessed subjectively by the subjects in the natural setting or by a polysomnograph in the laboratory.

Sample size
Sample size calculations in the studies were based on SDs of the primary efficacy variable of 25-35 minutes (depending on the study), a 2-sided t-test with a significance level of 0.05 adjusted for multiple comparisons with the Bonferroni Procedure, and 20% missing observations. With an expected effect size of 12 minutes in favour of the active arm, the power of the different studies ranged between 80-90%.

Statistical methods
The primary efficacy analysis used a modified intent-to-treat (ITT) population consisting of all subjects who were randomized, received at least 1 dose of double-blind medication during the study, and had baseline measure (except the crossover studies and the healthy volunteer studies which had no baseline measures) and at least one post-baseline (sleep latency) measure.

Analysis of efficacy was done using analysis of variance (ANOVA) in the crossover and healthy volunteer studies and using analysis of covariance (ANCOVA; with baseline measures as covariate) in the other studies. Comparisons between the treatments were made using t-tests with Least Square (LS) means and standard errors obtained from the ANOVA or ANCOVA models.

Statistical significance was corrected for multiple comparisons by the Dunnett procedure and Fisher protected Least Significant Difference (LSD).

- Main studies

A short description of the design of the different studies is provided below.

TL020 & TL025: These two studies, TL020 in adults and TL025 in elderly subjects, were conducted entirely in an outpatient setting. The double blind period consisted of 35 nights.
After initial screening subjects were entered into a second phase which included 7 consecutive nights with single blind placebo. During this latter period, subjects had to record sleep parameters in a sleep diary. The following inclusion criteria had to be met:

- Chronic insomnia as defined by DSM-IV for the past 3 months ascertained by subjective reporting
- subjective sleep latency (sSL) >= 45 minutes
- subjective total sleep time (sTST) <= 6.5 hours per night for at least 3 nights during the week of the single blind lead-in period, based on the sleep diary
- daytime complaints associated with disturbed sleep

Subjects who met inclusion criteria were randomized to receive ramelteon 8 or 16 mg or placebo (TL020) or 4 or 8 mg or placebo (TL025) for a total of 35 nights. Throughout the course of the study, subjects were asked to maintain daily diaries and return to the clinic weekly for CGIs, and review of diaries, concomitant medications, and adverse events.
The 35 night double-blind period was followed by single blind placebo period of 7 consecutive nights and was designed to assess possible rebound insomnia and withdrawal effects (see section pharmacodynamic).

The primary efficacy variable was the average subjective sleep latency based on the sleep diary over the first week of double blind treatment. Results from the other weeks were defined as secondary outcome variables.

CCT002: This efficacy and safety study in 1130 Japanese adult and elderly subjects with a diagnosis of chronic insomnia consisted of two periods of 14 days each.
In order to ascertain inclusion/exclusion criteria for this study subjects were first screened and then entered into the second screening phase, which included 7 consecutive nights with single blind placebo. During this period, and throughout the study, subjects had to record sleep parameters in a sleep diary. The following inclusion criteria had to be met:

- Chronic insomnia as defined by DSM-IV for the past 3 months ascertained by subjective reporting
- subjective sleep latency (sSL) >= 45 minutes
- subjective total sleep time (sTST) <= 6.5 hours per night for at least 3 nights during the week of the single blind lead-in period, based on the sleep diary
- daytime complaints associated with disturbed sleep

Subjects who met inclusion criteria were randomized to receive double blind placebo, ramelteon 4 or 8 mg for a total of 14 nights. This was followed by another 14-night, double-blind treatment period with dose escalation to 4, 8, and 16mg, respectively. Throughout the course of the study, subjects were asked to maintain daily diaries and return to the clinic weekly for CGIs, and review of diaries, concomitant medications, and adverse events.
The 28-night double-blind period was followed by single blind placebo period of seven consecutive nights and was designed to assess possible rebound insomnia and withdrawal effects.
The primary efficacy variable was the average subjective sleep latency based on the sleep diary over the first week of double blind treatment.

TL021: In this parallel groups study, subjects first spend 2 nights in a sleep laboratory with placebo run-in and PSG measures, followed by a 5-day outpatient period of single-blind placebo dosing. The randomised phase (with placebo or ramelteon 8 or 16 mg) consisted of 35 nights. During this period, each subject had a total of 3 sessions of 2 consecutive nights in the sleep laboratory in which PSG recordings were made. This was on nights 1-2, 15-16, and 29-30. On all other nights, subjects were asked to maintain daily sleep diaries. After the 35 nights of double-blind treatment, subjects again reported to the sleep laboratory for 2 consecutive nights (36 and 37) of PSG recordings with single-blind placebo. Final evaluations and completion of the study occurred on Day 38.
The primary outcome variable was defined as mean latency to persistent sleep on nights 1&2.

EC301: This study included zopiclone, in addition to placebo, as an active control arm. The study's aim was to examine the effect of ramelteon on balance in adults with chronic insomnia but included measures of efficacy as well. After screening and single blind placebo run-in period, subjects were included if they met the following inclusion criteria:

- meeting criteria for chronic insomnia
- subjective sleep latency (sSL) ≥45 minutes
- subjective total sleep time (sTST) ≤6.5 hours
- mean LPS of ≥20 minutes on 2 consecutive screening nights in the laboratory with PSG

They were randomised to receive nightly doses of 8 mg ramelteon, 7.5 mg Zopiclone, or placebo for a period of 28 nights. The double-blind period included two sessions of 2-night PSG assessment on Nights 1 to 2 and 27 to 28 and a balance assessment on Night 14.
Primary outcome variable in this study was the safety evaluation (balance) on night 14.

EC302: Inclusion criteria for this long-term study consisted of:

- Chronic insomnia as defined by DSM-IV for the past 3 months ascertained by subjective reporting
- subjective sleep latency (sSL) >= 45 minutes,
- subjective total sleep time (sTST) <= 6.5 hours per night
- daytime complaints associated with disturbed sleep
- Subject who met these initial criteria were then entered into the second screening phase which included 2 consecutive polysomnographic (PSG) nights in a sleep centre with single blind placebo in which they had to have a mean sleep latency (SL) > 20 minutes

Eligible subjects were randomised to either ramelteon 8 mg or placebo for a period of 6 months. During this treatment period, subjects reported to the sleep laboratory for objective assessment of sleep parameters using PSG. These assessments occurred on the first 2 nights of double blind treatment and at the end of Months 1, 3, 5, and 6. The primary efficacy variable was mean sleep latency of 2-night PSG at Month 3 and then Month 6.
Following the double-blind treatment, subjects reported to the sleep laboratory for PSG recordings over 2 nights while receiving single-blind placebo medication. Placebo medication was then given to subjects to take nightly over a 12-day period. Rebound insomnia and withdrawal were assessed during this period.

Studies TL005, TL017, and CCT001: In these three crossover studies, each subject was randomized to a treatment sequence that included several different doses of ramelteon and placebo in a certain sequence, e.g. in TL017 subjects received sequences of four different doses of ramelteon and placebo. Following the screening phase, all qualified subjects checked into a sleep centre at approximately 2 to 2.5 hours before their habitual bedtime. A study medication was administered 30 minutes before habitual bedtime on two consecutive polysomnography (PSG) nights in a sleep centre. After each treatment period, subjects underwent a 5- or 12-day washout period before returning to the sleep centre and commencing the next dosing sequence.

PNFP002 and **TL023:** These studies examined the efficacy and safety of a single dose ramelteon 16 and 64 mg (PNFP002) or 8 and 16mg (in TL023) compared to placebo in healthy volunteers. Subjects were included if they reported a usual sleep time between 6.5 and 8.5 hours and sleep latency ≤ 30 minutes.
Subjects were randomised to receive a single dose of study medication to be administered prior to the habitual bedtime in a sleep laboratory. The primary outcome variable was defined as latency to persistent sleep as measured by PSG.

During the assessment, the CHMP requested the applicant to perform responder analyses to improve the understanding of the clinical relevance of the efficacy results. In two analyses performed, the applicant defined as response sleep latency <= 30 minutes or a reduction of >=50% from baseline.

RESULTS

Disposition of patients
Disposition of subjects is summarised in the table below.

Table 3 Number of patients randomised, number of completers and reasons for withdrawal

Study (duration)		**Placebo**	**Ramelteon 4mg**	**Ramelteon 8mg**	**Ramelteon 16mg**
STUDIES IN NATURAL SETTING					
TL020 (35 nights)	Randomised	287		277	284
	Completed	242 (84%)		232 (84%)	238 (84%)
	Withdrew	45		45	46
	LOF	9 (3.1%)		10 (3.6%)	5 (1.8%)
	AE	7 (2.4%)		6 (2.2%)	12 (4.2%)
TL025 (35 nights, elderly)	Randomised	274	281	274	
	Completed	228 (83%)	234 (83%)	239 (87%)	
	Withdrew	46	47	35	
	LOF	17 (6.2%)	14 (5.0%)	9 (3.3%)	
	AE	8(2.9%)	8 (2.8%)	7(4.4%)	
SLEEP LABORATORY STUDIES					
TL021 (35 nights)	Randomised	131		139	135
	Completed	119 (91%)		124 (89%)	128 (95%)
	Withdrew	12		15	7
	LOF	2 (1.5%)		0	0
	AE	2 (1.5%)		3 (2.2%)	1 (0.7%)
EC301 (28 nights)	Randomised	94	**Zopiclone:** 93	88	
	Completed	89 (95%)	80 (86%)	80 (91%)	
	Withdrew	5	13	8	
	LOF	0	0	2 (2.3%)	
	AE	0	3 (3.2%)	1 (1.1%)	
EC302 (6 month adults & elderly)	Randomised	224		227	
	Completed	176 (79%)		159 (70%)	
	Withdrew	48		68	
	LOF	4 (1.8%)		1 (0.4%)	
	AE	10 (4.5%)		7 (3.1%)	
Sleep laboratory studies: crossover design					
TL005 (crossover)	Randomised	106			
	Completed	103 (97%)			
	Withdrew	3			
	LOF/AE	0/0			
TL017 (crossover, elderly)	Randomised	100			
	Completed	100			
	Withdrew				
	LOF/AE				
CCT001 (crossover, Japanese)	Randomised	65			
	Completed	60 (62%)			
	Withdrew	5			
	LOF	0			
	AE	3 (5%)			
Sleep laboratory studies: Healthy volunteers					
PNFP002 (healthy volunteers)	Randomised	123	126		**Ramelteon 64** 126
	Completed	123	126		126
	Withdrew	0	0		0
	LOF/AE	0/0	0/0		0/0
TL023 (healthy volunteers)	Randomised	97		98	94
	Completed	96 (99%)		98	94
	Withdrew	1		0	0
	LOF/AE	0/ 1 (1%)		0/0	0/0
	LOF	17 (6.2%)	14 (5.0%)	9 (3.3%)	
	AE	8(2.9%)	8 (2.8%)	7(4.4%)	

Study CCT002 not included in this table as only preliminary results reported for this study; LOF =lack of efficacy; AE= adverse event

Table 4 below presents the results of all studies in terms of the primary endpoint (in bold; results in other time points are presented in normal print).

Table 4 Primary efficacy endpoint[a] and longer duration effect: mean latency to persistent sleep, ITT population

Study/ Treatment Group	N (randomised)	Least Squares Mean Baseline(sd)	Least Squares Mean Endpoint (SD)	Treatment Comparisons Difference from placebo (SD)	95% CI	P-value[c]
STUDIES IN NATURAL SETTING						
TL020 (35 nights)			**WEEK 1**			
Placebo	283	85.5 (50.3)	**74.4 (36,5)**			
Ram 8 mg	270	85.2 (49.8)	**74.8 (36,2)**	**0.4 (49.5)**	**-5.5 , 6.3**	**0.888**
Ram 16 mg	276	92.5 (49.5)	**77.2 (36.1)**	**2.8 (49.8)**	**-3.1 , 8.7**	**0.349**
			WEEK 5			
Placebo			66.5 (2.16)			
Ram 8 mg			64.1 (2.20)	-2.3 (3.00)	-8.2 , 3.6	0.436
Ram 16 mg			65.2 (2.17)	-1.3 (2.99)	-7.2 , 4.6	0.665
TL025 (35 nights)			**WEEK 1**			
Placebo	274	84.2 (51.8)	**78.5 (37.1)**			
Ram 4 mg	281	83.5 (51.5)	**70.2 (37.1)**	**-8.3 (51.3)**	**-14.4 , -2.2**	**0.008**
Ram 8 mg	273	86.6 (51.6)	**70.2 (37.0)**	**-8.3 (52.3)**	**-14.5 , -2.2**	**0.008**
			WEEK 5			
Placebo			70.6 (2.36)			
Ram 4 mg			63.4 (2.32)	-7.1 (3.25)	-13.5 , -0.8	0.028
Ram 8 mg			57.7 (2.36)	-12.8 (3.28)	-19.3 , -6.4	<0.001
CCT002 (28 nights)			**WEEK 1**			
Placebo	380	79.9 (2.25)	**64.5 (1.29)**			
Ram 4 mg	372	83.3 (2.27)	**64.7 (1.31)**	**0.2 (35.4)**	**(-3.4 , 3.8)**	**0.93**
Ram 8 mg	378	77.5 (2.25)	**61.4 (1.29)**	**-3.1 (35.5)**	**(-6.7 , 0.5)**	**0.09**
			WEEK 2			
Placebo			57.9 (1.33)			
Ram 4 mg			57.9 (1.35)	-0.06 (nr)	nr	nr
Ram 8 mg			57.5 (1.35)	-0.47 (nr)	nr	nr
			WEEK 3			
Ram 4 mg			51.5 (1.39)			
Ram 8 mg			53.9 (1.41)	2.4 (nr)	nr	nr
Ram 16 mg			52.4 (1.40)	0.9 (nr)	nr	nr
			WEEK 4			
Ram 4 mg			47.9 (1.43)			
Ram 8 mg			51.9 (1.46)	4.0 (nr)	nr	nr
Ram 16 mg			48.8 (1.45)	0.9 (nr)	nr	nr
Studies in laboratory setting						
TL021 (35 days)			**NIGHTS 1&2**			
Placebo	131	65.3 (40.5)	**47.9 (31.1)**			
Ram 8 mg	139	64.3 (40.9)	**32.2 (31.5)**	**-15.7 (43.6)**	**-22.9 , -8.4**	**<0.001**
Ram 16 mg	135	68.4 (41.1)	**28.9 (31.5)**	**-18.9 (43.3)**	**-26.3 , -11.6**	**<0.001**
			NIGHTS 29&30			
Placebo			42.5 (2.97)			
Ram 8 mg			31.5 (2.91)	-11.0 (4.03)	-18.9 , -3.1	0.007
Ram 16 mg			29.5 (2.96)	-12.9 (4.07)	-20.9 , -4.9	0.002
EC301 (safety)			**NIGHTS 1&2**			
Placebo	94	67.9 (45.8)	**40.6 (30.3)**			
Ram 8 mg	88	67.8 (39.2)	**30.8 (30.2)**	**-9.7 (43.3)**	**-18.5 , -0.9**	**0.031**
Zopiclone 7.5 mg	93	56.4 (30.3)	**34.5 (30.4)**	**-6.1 (41.2)**	**-14.8 , 2.7**	**0.171**
			NIGHTS 27&28			
Placebo	94	67.9 (45.8)	31.2 (29.5)			
Ram 8 mg	88	67.8 (39.2)	29.2 (29.5)	-1.9 (42.4)	-10.5 , 6.7	0.658
Zopiclone 7.5 mg	93	56.4 (30.3)	37.1 (29.6)	5.9 (40.7)	-2.6 , 14.5	0.173

Study/ Treatment Group	N (randomised)	Least Squares Mean Baseline(sd)	Least Squares Mean Endpoint (SD)	Treatment Comparisons Difference from placebo (SD)	95% CI	P-value[c]
EC302 (6 month)			**NIGHTS 1&2**			
Placebo	224		**46.7 (36.9)**	**-14.7 (2.66)**	**-19.9 , -9.4**	**0.001**
Ram 8 mg	227		**32.0 (29.5)**			
			END MONTH 3			
Placebo	224	69.6 (42.6)	37.1 (29.3)			
Ram 8 mg	227	70.8 (41.4)	30.7 (29.2)	-6.4 (42.2)	-11.8 , -1.0	0.021
			END MONTH 6			
Placebo	224	69.6 (42.6)	39.8 (32.9)			
Ram 8 mg	227	70.8 (41.4)	30.9 (32.9)	-8.9 (46.7)	-14.9 , -2.9	0.004
Sleep laboratory studies: crossover design						
TL005	107	75.2 (40.2)	**NIGHTS 1&2**			
Placebo			38.1 (35.4)			
Ram 4 mg			24.5 (21.6)	-13.7 (35.4)	(-20.4, -7.0)	<0.001
Ram 8 mg			24.6 (21.7)	-13.4(35.1)	(-20.0, -6.7)	<0.001
Ram 16 mg			24.2 (22.3)	-13.7(35.4)	(-20.4, -7.0)	<0.001
Ram 32 mg			23.2 (22.5)	-14.8(35.4)	(-21.5, -8.1)	<0.001
TL017	100	54.4 (33.2)	**NIGHTS 1&2**			
Placebo			38.4 (24.5)			
Ram 4 mg			28.7 (23.8)	-9.7 (26.4)	-14.9 , -4.5	<0.001
Ram 8 mg			30.8 (25.2)	-7.6 (27.0)	-12.9 , -2.3	<0.001
CCT001(Japan)	65	61.8 (38.9)	**NIGHTS 1&2**			
Placebo			36.0 (40.7)			
Ram 4 mg			29.5 (28.5)	-6.5 (32.8)	(-14.7, 1.6)	0.27
Ram 8 mg			22.5 (18.2)	-13.5 (39.2)	(-23.2, -3.8)	0.02
Ram 16 mg			29.0 (29.4)	-7.1 (33.4)	(-15.4, 1.2)	0.23
Ram 32 mg			25.0 (32.8)	-11.0 (28.0)	(-18.0, -4.1)	0.01
Sleep laboratory studies: Healthy volunteers						
PNFP002			**1 NIGHT**			
Placebo	123	13.3 (6.4)*	**22.6 (21.9)**			
Ram 16 mg	126	13.2 (7.4)	**12.2 (15.1)**	**-10.4 (28.1)**	**-15.3 , -5.5**	**<0.001**
Ram 64 mg	126	13.2 (9.1)	**13.4 (15.4)**	**-9.2 (28.1)**	**-14.1 , -4.3**	**<0.001**
TL023			**1 NIGHT**			
Placebo	97	14.8 (7.1)*	**19.7 (18.4)**			
Ram 8 mg	98	14.6 (6.4)	**12.2 (18.6)**	**-7.6 (25.8)**	**-12.7 , -2.4**	**0.004**
Ram 16 mg	93	14.4 (6.3)	**14.8 (18.6)**	**-4.9 (26.2)**	**-10.1 , 0.3**	**0.065**

[a] primary efficacy endpoints are denoted in bold.

* Baseline measures of sleep latency are based on subjectively reported data and hence are not comparable to PSG values. In these 2 studies there was no adjustment for baseline values in the statistical analysis.

c p-values for comparisons were adjusted by Dennett's method

Table 5 below presents the results in terms of the secondary endpoints

Table 5 Secondary efficacy variables: PSG vs. sleep diary: sleep laboratory studies

		Least Squares		Treatment Comparisons		
Study/ Treatment Group	**N** (randomised)	**Mean Baseline(sd)**	**Mean Endpoint (SD)**	**Difference from placebo (SD)**	**95% CI**	**P-value[c]**
TL021 (35 days)						
	LATENCY TO PERSISTENT SLEEP - PSG					
			Nights 1&2			
Placebo	131	65.3 (40.5)	47.9 (31.1)			
Ram 8 mg	139	64.3 (40.9)	32.2 (31.5)	-15.7 (43.6)	-22.9 , -8.4	<0.001
Ram 16 mg	135	68.4 (41.1)	28.9 (31.5)	-18.9 (43.3)	-26.3 , -11.6	<0.001
			nights 29&30			
Placebo			42.5 (34.0)			
Ram 8 mg			31.5 (34.3)	-11.0 (47.5)	-18.9 , -3.1	0.007
Ram 16 mg			29.5 (34.4)	-12.9 (47.3)	-20.9 , -4.9	0.002
	Subjective sleep latency (sSL): sleep diary and questionnaires					
			Week 1			
Placebo		74.7 (41.9)	64.3 (27.2)			
Ram 8 mg		71.4 (42.2)	62.9 (27.6)	-1.4 (38.2)	-7.8 , 5.0	0.665
Ram 16 mg		77.8 (42.3)	59.7 (27.7)	-4.6 (38.0)	-11.0 , -1.8	<0.159
			Week 5			
Placebo			57.1 (27.3)			
Ram 8 mg			52.5 (27.1)	-4.6 (37.6)	-10.8 , 1.7	0.153
Ram 16 mg			53.5 (27.2)	-3.6 (37.4)	-9.9 , 2.7	0.262
	Subjective sleep latency (sSL): only questionnaires					
			Week 1			
Placebo		77.0 (42.8)	70.2 (43.5)			
Ram 8 mg		78.5 (43.2)	52.9 (44.0)	-17.3 (60.7)	-27.4 , -7.2	<0.001
Ram 16 mg		75.2 (43.8)	56.3 (45.2)	-13.9 (61.2)	-24.2 , -3.5	0.009
			week 5			
Placebo			61.5 (42.6)			
Ram 8 mg			44.8 (42.9)	-16.7 (59.5)	-26.6 , -6.7	0.001
Ram 16 mg			53.8 (43.6)	-7.7 (59.6)	-17.8 , 2.4	0.134
EC301 (safety)						
	LATENCY TO PERSISTENT SLEEP - PSG					
			Nights 1&2			
Placebo	94	67.9 (45.8)	40.6 (30.3)			
Ram 8 mg	88	67.8 (39.2)	30.8 (30.2)	-9.7 (43.3)	-18.5 , -0.9	0.031
Zopiclone 7.5 mg	93	56.4 (30.3)	34.5 (30.4)	-6.1 (41.2)	-14.8 , 2.7	0.171
			nights 27&28			
Placebo			31.2 (29.5)			
Ram 8 mg			29.2 (29.5)	-1.9 (42.4)	-10.5 , 6.7	0.658
Zopiclone 7.5 mg			37.1 (29.6)	5.9 (40.7)	-2.6 , 14.5	0.173
	Subjective sleep latency (sSL): only questionnaires					
			Nights 1&2			
Placebo		78.9 (43.2)	58.5 (31.7)			
Ram 8 mg		73.0 (44.8)	50.2 (31.7)	-8.3 (44.2)	-17.6 , 1.0	0.079
Zopiclone 7.5 mg		69.1 (43.7)	40.73 (31.7)	-17.8 (44.8)	-26.9 , -8.6	<0.001
			nights 27&28			
Placebo			44.4 (37.7)			
Ram 8 mg			48.5 (37.8)	4.1 (52.30)	-6.9 , 15.1	0.465
Zopiclone 7.5 mg			36.4 (37.9)	-8.1 (53.4)	-19.0 , 2.8	0.146

The results presented in table 4 pertain to only one aspect of sleep – sleep latency. Other aspects like maintaining sleep, and early morning awakening are components of insomnia as well and are more prominent in elderly compared to younger adults. However, the results obtained on these secondary efficacy variables (shown in table 5) were not supportive of a general effect on sleep. In response to this weakness in the submitted evidence, it was also considered to limit the indication to the treatment of sleep latency instead of insomnia.

The results with respect to sleep latency that are presented in table 4 indicate that only one of the three trials that were conducted in a natural setting (study TL025) obtained statistically significant effect on the primary endpoint. The effect in this trial, however, is small i.e. both dose groups had an advantage

of about 8 minutes above placebo (95% CI between 2 and 14 minutes). The reduction of 8 minutes in latency is small and of doubtful clinical relevance, especially considering that it results from a reduction in latency from 78 minutes in the placebo treated subjects compared to latency of 70 minutes in the active group, hence proportionally a small improvement. A positive control with an established sleep medication would have been helpful to assess the relevance of this difference but this was not available.
Furthermore, in some of the studies (i.e. in sleep laboratory studies) sleep latency that was obtained in the first week of treatment diminished over time. The proposal to limit the duration of treatment to 5 weeks was also considered by the CHMP; however, diminishing effects were seen within this period as well.

In the two other natural setting studies, the effect was minimal (less than 1 minute and less than 3 minutes difference in latency of the two dose groups, respectively compared to placebo) and not statistically significant. As these studies did not include a positive control arm, it is impossible to disentangle whether the lack of efficacy is due to a true lack of effect (negative study) or due to lack of assay sensitivity (failed studies).

The applicant disagreed that only three trials were conducted in the natural settings. It was argued that components of the sleep laboratory studies included sleeping in the natural setting and that sleep latency results form these parts of the studies should also be considered. However, an examination of the available evidence indicated that only one of the three sleep laboratory studies (TL021) did in fact contain measurement of sleep latency relating to sleep in the natural setting. Subjective sleep latency in TL021 was measured in two ways: one was based on sleep diaries, the other on post sleep questionnaires (PSQ). The assessment via diaries showed minor and non-significant effects while assessment via PSQ showed larger and statistically significant effects. Specifically, advantage in term of sleep latency of ramelteon 8mg vs. placebo was about 17 minutes during the whole assessment period and of ramelteon 16mg it was 14, 12, and 8 minutes in weeks 1, 3, and 5 respectively.
There are some doubts regarding the validity of newly presented results, as in study TL021 a large proportion of patients were randomised despite they didn't meet the inclusion criteria, as demonstrated by the high proportion (61.5%) of ITT subjects excluded from the PP population.

To address the issue of clinical relevance of the obtained effect, the applicant was asked to provide a responders analysis. In one analysis response was defined as sleep latency <= 30 minutes. The applicant claimed that this criterion had been endorsed as clinically relevant by a group of clinical experts. In addition, spending less than 30 minutes falling asleep is considered as normal by e.g. insomnia questions in the HAMD. Statistically significant results were achieved when pooled data were presented taking into consideration only two of the main studies conducted in the natural setting along with data from laboratory studies. When only the main clinical studies were analysed, the following non significant results were obtained, in TL020 the percentage of responders was 11.9 (ramelteon 8 mg) *versus* 12.0 for placebo (p-value 0.659), and in TL025 the percentage of responders was 17.5 and 15.8 (ramelteon 4mg and 8 mg respectively) *versus* 15.3 for placebo (p-value 0.353, 0.731).
When the response was defined as a reduction of >=50% from baseline in sleep latency, the results were for TL020 47% (ramelteon 8mg) *versus* 42% placebo (p-value 0.4403) and for TL025 51% and 44% (ramelteon 4mg and 8mg respectively) *versus* 34% for placebo (p-value 0.579, 0.2533).
Therefore, the applicant failed to show statistically significant differences between ramelteon and placebo in the proportion of responders.

With the responses to the questions raised by the CHMP, the applicant presented sleep latency results of external comparators: zaleplon and melatonin. These comparisons seem to suggest that improvement in latency that was found in the ramelteon studies (range 0-8 minutes) is lower with respect to that found with zaleplon (range 5-20) or melatonin (4.5-10). However, these comparisons, with no reference to the response rate, are of limited value as they do not address the clinical relevance of the effect.

Larger differences in sleep latency between active arms and placebo were observed in laboratory studies. In one study (TL021) an advantage of 16 and 19 minutes compared to placebo on the first 2

nights were observed in the 8 and 16 mg dose groups, respectively (both were statistically significant with confidence intervals ranging between 8 and 26 minutes). The second laboratory study showed a smaller advantage for ramelteon of 10 minutes (statistically significant). However, this advantage diminished on the longer term. It is also noted that the spontaneous improvement, as measured by change from baseline in these studies exceeded the treatment effect. Furthermore, the generalisability of this effect to the natural setting is questionable. An effect obtained in a laboratory study that cannot be translated to a subjective improvement by patients, may not be relevant.
It is noted that in study EC301 the active control arm (zopiclone) showed a smaller and non-significant effect suggesting that the validity of this study is at stake as zopiclone, given at the appropriate doses, does not evoke the expected response.

It is tempting to attribute the inconsistent results in the natural setting studies to the different population studied i.e. elderly in study TL025 compared to adults in the other two studies. After all, melatonin release and melatonin plasma levels decrease with ageing and thus melatonin receptor agonists may exert an effect. However, increased incidence of insomnia with aging and decrease in melatonin levels with aging may also be epiphenomena instead of causally related. Furthermore, melatonin levels were not investigated in the studies presented. Altogether, other factors besides age may be responsible for the significant effects in study TL025 and the hypothesis that age is the crucial factor would needs confirmation in a new study in the elderly.
The applicant was asked to investigate the likelihood of an effect that is specific to the elderly by performing an analysis stratified by age and to investigate whether this hypothesis is supported from a pharmacodynamic perspective (i.e. disturbed circadian rhythm and melatonin production in the elderly and effect of ramelteon on circadian rhythm).
The stratified analyses that was presented did not provide support for the hypothesis that ramelteon might be exclusively effective in the elderly. In addition, the applicant indicates that mixed results are found in the literature concerning the relationship between melatonin production and age and between melatonin level and sleep problems and therefore an age effect is not expected with regard to ramelteon.

Long-term efficacy: The results of laboratory study EC302 show that the difference between active arm and placebo diminishes on the long-term. This trend (also observable in other laboratory studies, i.e. TL021 and EC301/2) is due to the continued improved latency in the placebo group over time while latency in the actively treated group remains more or less constant. Hence, long-term treatment cannot be justified based on these results, as the evidence suggests that spontaneous improvement may be occurring. Considering to limit the treatment duration to five weeks would not be sufficient, in fact reduction of efficacy are seen event between week 1 and week 5.

Finally, it is noted that the lack of a dose response effect does not support efficacy. Furthermore, there is no justification of 4 mg as the minimal effective dose.

- Discussion on clinical efficacy

Altogether, it is considered that short and long-term efficacy of Ramelteon in the treatment of insomnia was not demonstrated.

Specifically, evidence of efficacy focused on only one aspect – sleep latency - while efficacy concerning other aspects (i.e. sleep quality, number of awakenings, early morning awakening, next day functioning) was not demonstrated.
In one of the three pivotal studies conducted in the natural setting (TL 025), more than 270 patients were enrolled for each of the three arms, placebo, ramelteon 4 and 8 mg. A statistically significant effect was demonstrated at week 1, with a difference from placebo of about 8 minutes and over a total time to sleep of about 78 minutes in the placebo arm and 70 minutes in the active arm. No effect dose relation was proven since the effect at 4 and 8 mg was the same. In the other two studies, more than 270 patients (TL 020) and more than 370 (CCT002) patients entered each arm (ramelteon 16 mg was also administered), but no statistical significance was achieved for latency to sleep. Therefore the results obtained in the natural setting did not confirm the positive results of the laboratory studies.

Even if an indication for sleep latency only would be sought, a statistical significant improvement in sleep latency was observed in only one of the three pivotal trials that were conducted in the natural setting. Additional evidence that was submitted in support of an effect on sleep latency in the natural setting comes from trials where a large proportion of the initially screened patients dropped out after randomisation. More importantly, the clinical relevance of the difference obtained in sleep latency is questionable. Finally, long-term efficacy was not demonstrated, as latency results on the longer-term show increased improvement in the placebo arms while latency in the active arms remains constant and hence the difference becomes smaller.

In addition to the fact that minimal changes in sleep latency were observed, there are changes in sleep architecture showing an increase in light sleep at the expense of deep sleep. This is an unexpected result for a sleep medication, which has not been adequately explained. Another weakness of this dossier is the fact that there was no adequate justification for the dose.

Considering the responder analyses, when the definition of responder is sleep latency <= 30 minutes, this remains a post-hoc formulation as no mention of responders definition was found in the protocol.
Furthermore, results are presented only for 2 of the three studies that were conducted in the natural setting (i.e. for studies TL020 and TL025, but not for CCT002). Results for these two studies show no difference between ramelteon and placebo treated patients in percentage of responders. Hence, these results do not support the clinical relevance of the effect on the mean improvement in latency time.
Also when the response was defined as a reduction of >=50% from baseline in sleep latency, responder analysis showed no significant difference between ramelteon and placebo in the natural setting studies, therefore it is concluded clinical relevant difference was not demonstrated.

Clinical safety

Safety of ramelteon was assessed in all subjects who participated in any study, controlled and uncontrolled.
Special attention was given to safety issues typically associated with hypnotic compounds, specifically, abuse potential, withdrawal/ rebound effects, next-morning effects, psychomotor or memory impairment, and risk of falls.

- Patient exposure

A total of 6,206 subjects have participated in 55 clinical trials of ramelteon.

The number of subjects exposed by type of study and duration is presented in the table below.

Table 6 Number of subjects exposed by study type and duration

Study type	Placebo	Ramelteon	Total
Total[(a)]	2051	5145	6206
Placebo-controlled studies in subjects with insomnia[(b)]	1233	1937	3170
Study duration			
< 7 days	425	653	1078
8 to 35 days	963	1671	2634
6 months[(b)]	65	57	122
12 months (open label study)	–	1213	1213
Active comparator studies[(a)]	157	151	308
Placebo-controlled studies with healthy volunteers	220	444	664
Clinical pharmacology			
Placebo-controlled	148	235	235
Open-label	–	683	683
Special safety studies	–	223	223
Studies in Japanese subjects	103	190	293

(a) At least one exposure to ramelteon. Some subjects are counted for both ramelteon and placebo.
(b) Integrated analyses do not included the 228 subjects exposed to ramelteon 8 mg in the 6 month controlled study EC302, which was completed after the safety database lock.

Note: In addition to the subjects who received either placebo or ramelteon, 123 subjects received zopiclone and 33 subjects received zolpidem in crossover design studies.

All subjects in the ramelteon development program were 18 years or older, with 623 subjects 65 to 74 years (elderly), and 281 subjects were 75 years or older (older elderly). A total of 1,213 subjects were enrolled in an uncontrolled, long-term study of whom 473 received ramelteon for 12 months. The randomised controlled studies included subjects with primary insomnia that has lasted for over 3 month. A few studies investigated efficacy and safety in healthy volunteers, in a transient insomnia model.
In most studies, ramelteon doses of 8 and 16 mg were administered to adults (≥18 to <64 years) while doses of 4 and 8 mg were administered to elderly subjects (≥65 years).

- Adverse events

The incidence of the most commonly reported treatment emergent adverse events occurring in placebo-controlled trials in subjects with chronic insomnia is presented in the table below. Ramelteon 4 and 8 mg is the recommended dose.

Table 7 Treatment emergent adverse events occurring in ≥2% of subjects with insomnia

	Number (%) of Subjects					
		Ramelteon				
Preferred Term	**Placebo (n = 1233)**	**4 mg (n = 486)**	**8 mg (n = 1177)**	**16 mg (n = 585)**	**32 mg (n = 105)**	**All Doses (n = 1937)**
Any adverse event	506 (41.0)	187 (38.5)	475 (40.4)	288 (49.2)	21 (20.0)	926 (47.8)
Headache	84 (6.8)	22 (4.5)	92 (7.8)	63 (10.8)	6 (5.7)	176 (9.1)
Somnolence	29 (2.4)	12 (2.5)	43 (3.7)	41 (7.0)	2 (1.9)	97 (5.0)
Dizziness	40 (3.2)	21 (4.3)	45 (3.8)	11 (1.9)	0	77 (4.0)
Fatigue	25 (2.0)	6 (1.2)	40 (3.4)	18 (3.1)	2 (1.9)	65 (3.4)
Insomnia	26 (2.1)	7 (1.4)	34 (2.9)	24 (4.1)	0	65 (3.4)
Nausea	28 (2.3)	11 (2.3)	31 (2.6)	22 (3.8)	1 (1.0)	62 (3.2)
Nasopharyngitis	37 (3.0)	8 (1.6)	24 (2.0)	19 (3.2)	1 (1.0)	52 (2.7)
Myalgia	13 (1.1)	15 (3.1)	20 (1.7)	10 (1.7)	1 (1.0)	46 (2.4)

Treatment emergent AEs that were considered by the investigator to be of severe intensity and occurred in ≥ 2 subjects in ramelteon treatment groups in placebo-controlled trials with subjects with chronic insomnia are presented in the table below.

Table 8 Treatment emergent severe AEs occurring in ≥ 2 in ramelteon treatment group in studies with subjects with insomnia

	Number of Subjects					
		Ramelteon				
Preferred Term	**Placebo (n = 1233)**	**4 mg (n = 486)**	**8 mg (n = 1177)**	**16 mg (n = 585)**	**32 mg (n = 105)**	**All Doses (n = 1937)**
Any AE n (%)	506 (41.0)	187 (38.5)	475 (40.4)	288 (49.2)	21 (20.0)	926 (47.8)
Any severe AE n (%)	56 (4.5)	15 (3.1)	41 (3.5)	37 (6.3)	0	93 (4.8)
Headache	6 (0.5)	2 (0.4)	6 (0.5)	7 (1.2%)	0	15 (0.8%)
Dizziness	0	4 (0.8)	5 (0.4)	0	0	9 (0.5)
Fatigue	2 (0.2)	1 (0.2)	3 (0.3)	4 (0.7)	0	8 (0.4)
Insomnia	6 (0.5)	0	5 (0.4)	2 (0.3)	0	7 (0.4)
Hyperacusis	0	0	5 (0.4)	1 (0.2)	0	6 (0.3)
Myalgia	2 (0.2)	3 (0.6)	3(0.3)	0	0	6 (0.3)
Nausea	3 (0.2)	1 (0.2)	0	3 (0.5)	0	4 (0.2)
Paresthesia	1 (0.1)	1(0.2)	2 (0.2)	1 (0.2)	0	4(0.2)
Somnolence	2 (0.2)	0	1 (0.1)	3 (0.5)	0	4(0.2)
Eye pain	1 (0.1)	0	2 (0.2)	1 (0.2)	0	3(0.2)
Photophobia	2 (0.2)	0	3(0.3)	0	0	3(0.2)
Muscle spasms	0	3 (0.6)	0	0	0	3 (0.2)
Arthralgia	0	0	2 (0.2)	0	0	2 (0.1)
Blood triglycerides increased	0	0	2 (0.2)	0	0	2 (0.1)
Derealization	0	0	2 (0.2)	0	0	2 (0.1)
Diarrhea	3 (0.2)	0	0	2 (0.3)	0	2 (0.1)
Dysgeusia	2 (0.2)	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Muscle twitching	0	0	2 (0.2)	0	0	2 (0.1)
Migraine	1 (0.1)	0	0	2 (0.3)	0	2 (0.1)
Nasopharyngitis	0	0	2 (0.2)	0	0	2 (0.1)
Vascular disorders	0	0	0	2 (0.3)	0	2 (0.1)

Special attention was paid to CNS and psychiatric related AEs because of their association to other sleep agents. A summary of these AEs occurring with greater frequency in ≥2 of the ramelteon groups compared with the placebo treatment group is provided in Table 9 below.

Table 9 Treatment emergent CNS AEs occurring in ≥2 in ramelteon treatment group in studies with subjects with insomnia

	Number (%) of Subjects					
		Ramelteon				
SOC Preferred Term	**Placebo (n = 1233)**	**4 mg (n = 486)**	**8 mg (n = 1177)**	**16 mg (n = 585)**	**32 mg (n = 105)**	**All Doses (n = 1937)**
Nervous system disorders	185 (15.0)	76 (15.6)	190 (16.1)	108 (18.5)	10 (9.5)	371 (19.2)
Headache	84 (6.8)	22 (4.5)	92 (7.8)	63 (10.8)	6 (5.7)	176 (9.1)
Somnolence	29 (2.4)	12 (2.5)	43 (3.7)	41 (7.0)	2 (1.9)	97 (5.0)
Dizziness	40 (3.2)	21 (4.3)	45 (3.8)	11 (1.9)	0	77 (4.0)
Dysgeusia	19 (1.5)	8 (1.6)	24 (2.0)	3 (0.5)	0	35 (1.8)
Paresthesia	10 (0.8)	6 (1.2)	9 (0.8)	3 (0.5)	0	18 (0.9)
Memory impairment	3 (0.2)	5 (1.0)	7 (0.6)	2 (0.3)	1 (1.0)	15 (0.8)
Lethargy	3 (0.2)	3 (0.6)	6 (0.5)	2 (0.3)	0	11 (0.6)
Parosmia	2 (0.2)	4 (0.8)	3 (0.3)	1 (0.2)	0	8 (0.4)
Sedation	2 (0.2)	3 (0.6)	6 (0.5)	1 (0.2)	1 (1.0)	8 (0.4)
Balance disorder	0	2 (0.4)	2 (0.2)	1 (0.2)	1 (1.0)	6 (0.3)
Migraine	2 (0.2)	1 (0.2)	0	5 (0.9)	0	6 (0.3)
Disturbance in attention	2 (0.2)	0	4 (0.3)	1 (0.2)	0	5 (0.3)
Restless leg syndrome	0	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Convulsion	0	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Psychiatric disorders	52 (4.2)	28 (5.8)	79 (6.7)	46 (7.9)	0	153 (7.9)
Insomnia	26 (2.1)	7 (1.4)	34 (2.9)	24 (4.1)	0	65 (3.4)
Depression	8 (0.6)	11 (2.3)	19 (1.6)	6 (1.0)	0	36 (1.9)
Anxiety	3 (0.2)	2 (0.4)	6 (0.5)	5 (0.9)	0	13 (0.7)
Derealization	2 (0.2)	4 (0.8)	9 (0.8)	0	0	13 (0.7)
Abnormal dreams	3 (0.2)	3 (0.6)	3 (0.3)	5 (0.9)	0	11 (0.6)
Nightmare	2 (0.2)	0	4 (0.3)	2 (0.3)	0	6 (0.3)
Restlessness	0	0	1 (0.1)	3 (0.5)	0	4 (0.2)
Agitation	0	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Confusional state	1 (0.1)	0	2 (0.2)	0	0	2 (0.1)
Depressed mood	0	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Disorientation	0	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Emotional disorder	0	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Hallucination	0	1 (0.2)	1 (0.1)	0	0	2 (0.1)
Mental disorder	0	1 (0.2)	1 (0.1)	0	0	2 (0.1)
Stress	0	1 (0.2)	1 (0.1)	0	0	2 (0.1)

- Serious adverse event/deaths/other significant events

Altogether 24 serious AEs (SAEs) occurred in the controlled studies that included subjects with insomnia, 15 (0.8%) in ramelteon treated subjects and 9 (0.7%) in placebo. These are listed in table 10 below.

As indicated in the table, one event, a transient Ischemic attack, occurring in a ramelteon treated subject, was considered possibly related to study drug.

Table 10 SAEs in placebo-controlled studies in subjects with chronic insomniac

	Placebo (n=1233)		Ramelteon (n=1937)	
	Related	**Not related**	**Related**	**Not related**
Amnesia				2
Arthritis				2
Atrial fibrillation		1		1
Cellulitis				1
Cholelithiasis				1
Convulsion				1
Dehydration				1
Diabetes mellitus				1
Diverticulitis		1		
Dizziness		1		
GI hemorrhage				1
Hyponatremia				1
Internal hernia				1
Jaw fracture		1		
Lung cancer		1		
Lung neoplasm		1		
Myocardial Ischemia		1		
Nausea				1
Pneumonia		1		
Syncope		1		
Transient Ischemic Attack			1	

Additional 2 SAEs occurred in the ramelteon arms of study EC301, with placebo and active (zopiclone) control arms. This amounted to a rate of 2.3% (2/88). Both events were classified as psychiatric disorders. One was an alcohol withdrawal syndrome, which was considered unrelated to study drug, the other was paranoid schizophrenia, which was considered to be possibly related to study drug. No SAEs were reported in either the placebo or in the zopiclone arms.

Additional SAEs occurred in the open label 12 month study. These are listed in table 11. Three of the events were considered as possibly related to study medication: 1 cerebrovascular accident, 1 prolactinoma, and 1 syncope.

No SAEs were reported in placebo-controlled studies with healthy volunteers (transient insomnia model) or in clinical-pharmacology studies.

Table 11 SAEs in open-label 12-Month Study

	Ramelteon 8mg (n= 248)			Ramelteon 16mg (n=1213)	
	Related	**Not related**		**Related**	**Not related**
Abdominal pain upper		1	Angina unstable		1
Benign prostatic hyperplasia		2	Arthritis NOS aggravated		1
Bladder cancer		1	Bladder prolapse		1
Cerebrovascular accident	1		Brain neoplasm NOS		1
Cervical myelopathy		1	Chest discomfort		1
Chest pain		1	Chest pain		1
Cholelithiasis		1	Cholelithiasis		1
Colon cancer NOS		1	Coronary artery occlusion		1
Coronary artery stenosis		1	Diverticulitis		1
Deep vein thrombosis		1	Duodenal ulcer perforation		1
Drug hypersensitivity		1	Ectopic pregnancy		1
ECG T-wave abnormal		1	Enterocele		1
Ovarian cyst		1	GERD		1
Pneumonia NOS		1	Head injury		1
Post procedural hemorrhage		1	Hiatus hernia		1
Spinal compression fracture		1	Inguinal hernia NOS		1
Wound infection		1	Intestinal Obstruction NOS		1
			Osteoarthritis NOS		1
			Prolactinoma	1	
			Syncope	1	
			Urinary tract infection		1
			Uterine fibroids		3
			Viral infection		1

Altogether, five SAEs were considered possibly related to study medication: transient Ischemic attack, paranoid schizophrenia, cerebrovascular accident, prolactinoma, and syncope. Four of these five had alternative medical explanations and risk factors. The subject who experienced transient ischemic attack had risk factors of age (age 72), hypertension and arteriosclerosis. The male patient with syncope was a long distance runner averaging 5 to10 miles several times per week with a history of bradycardia. The subject who experienced a cerebrovascular accident was 77 years old, had hypertension and concomitant medications included ibuprofen, acetaminophen, multivitamins, rabeprazole, fosinopril, and aspirin. The patient who experienced paranoid schizophrenia had a history of psychiatric treatment and had experience a clear emotional trigger for the event.

Two deaths occurred in the l2-month study (TL022) in subjects who received 16 mg ramelteon. The events that led to death involved in both cases motor vehicles accidents in which the victims were pedestrians. Neither event was considered related to the study drug. In one of the two cases, the accident occurred 7 days after the subject has discontinued participation in the study.
An additional death, by suicide, occurred in a placebo treated subject in a Japanese study.

- Laboratory findings

Hematology
The table below presents the number (%) of subjects in the clinical studies who had normal baseline hematology values and at least 1 markedly abnormal hematology test result (according to predefined criteria) during treatment.

Table 12: Subjects with markedly abnormal hematology values

	Placebo (n=897)	Ramelteon 4 mg (n=486)	Ramelteon 8 mg (n=896)	Ramelteon 16 mg (n=528)	Ramelteon 32 mg (n=105)	All Doses of Ramelteon (n=1599)
Hematocrit (%)						
M: ≤37%, F: ≤32%	9 (0.7%)	11 (2.3%)	7 (0.6%)	2 (0.3%)	0	20 (1.0%)
WBC (x10^3/uL)						
≤2.8	1 (0.1%)	0	1 (0.1%)	0	0	1 (0.1%)
Neutrophils (%)						
≤15%	1 (0.1%)	0	0	0	0	0
≥90%	1 (0.1%)	0	0	0	0	0
Lymphocytes (%)						
≤10%	4 (0.3%)	1 (0.2%)	2 (0.2%)	0	0	3 (0.2%)
Eosinophils (%)						
≥10%	3 (0.2%)	0	2 (0.2%)	2 (0.3%)	0	4 (0.2%)

Chemistry and urinalysis

Individual subject transitions for chemistry variables and urinalysis in placebo-controlled studies in subjects with insomnia indicate that only few subjects transitioned to out-of-range values and that no trends of clinical concern were observed with respect to the direction of these few transitions.

Blood pressure, heart rate, body weight, and ECG

The numbers (%) of subjects with prespecified abnormal changes from baseline in blood pressure, heart rate (measured by peripheral pulse), and body weight are summarized in table 13 below.

Table 13 Subjects with Prespecified Abnormal Changes in blood pressure, heart rate and body weight

		Number (%) of Ramelteon Subjects				All Doses of Ramelteon
	Placebo	4 mg	8 mg	16 mg	32 mg	
SBP (mm Hg)						
N	1203	479	1147	575	105	1890
≤90 and decrease ≥20	16 (1.3)	3 (0.6)	15 (1.3)	16 (2.8)	1 (1.0)	34 (1.8)
≥180 and increase ≥20	1 (0.1)	0	7 (0.6)	0	0	7 (0.4)
DBP (mm Hg)						
N	1203	479	1147	575	105	1890
≤50 and decrease ≥15	9 (0.7)	1 (0.2)	14 (1.2)	8 (1.4)	0	23 (1.2)
≥105 and increase ≥15	8 (0.7)	1 (0.2)	2 (0.2)	2 (0.3)	0	5 (0.3)
Heart rate (bpm)(a)						
N	1204	479	1146	576	105	1890
≤50 and decrease ≥15	9 (0.7)	5 (1.0)	14 (1.2)	10 (1.7)	0	29 (1.5)
≥120 and increase ≥15	1 (0.1)	0	0	0	0	0
Body weight (kg)						
N	482	68	428	175	0	671

		Number (%) of Ramelteon Subjects				All Doses of Ramelteon
	Placebo	4 mg	8 mg	16 mg	32 mg	
≥7% decrease	5 (1.0)	0	6 (1.4)	3 (1.7)	No data	9 (1.3)
≥7% increase	5 (1.0)	0	5 (1.2)	3 (1.7)	No data	5 (1.3)

The number of subjects with abnormalities related to vital signs that were reported as AEs is presented in table 14. The largest numbers of AEs reports in the all ramelteon group were palpitations and hypertension, with an incidence of 0.4% for both events, compared with 0.2% in the placebo group for both events.

Table 14 Vital Sign AEs Reported in Chronic Insomnia Studies

		Number (%) of Ramelteon Subjects				All Doses of Ramelteon
SOC	**Placebo**	**4 mg**	**8 mg**	**16 mg**	**32 mg**	**(n=1937)**
Preferred Term	**(n=1233)**	**(n=486)**	**(n=1177)**	**(n=585)**	**(n=105)**	
Palpitations	3 (0.2)	2 (0.4)	3 (0.3)	1 (0.2)	0	6 (0.3)
Hypertension NOS	2 (0.2)	2 (0.4)	3 (0.3)	0	0	5 (0.3)
Heart rate increase	3 (0.2)	0	3 (0.3)	0	0	3 (0.2)
Bradycardia NOS	0	1 (0.2)	1 (0.1)	0	0	2 (0.1)
Hypotension NOS	0	1 (0.2)	0	1 (0.2)	0	2 (0.1)
Syncope	3 (0.2)	0	1 (0.1)	1 (0.2)	0	2 (0.1)
Weight decrease	0	0	2 (0.2)	0	0	2 (0.1)
Tachycardia NOS	3 (0.2)	1 (0.2)	0	0	0	1 (0.1)
Weight increase	3 (0.2)	0	0	0	0	0

ECG

The number and percentages of subjects in insomnia studies with pre-specified abnormal change in QTc interval from baseline to the end of the double blind period and placebo run-out is provided in the table 15 below. QTc intervals were defined separate for males (<= 430, >430-450, >450-500. >500) and females (<= 450, >450-470, >470-500. >500).

Table 15 Number (%) of subjects in insomnia studies with pre-specified abnormal change in QTc interval from baseline

	Placebo	Ramelteon		
		4 mg	8 mg	16 mg
TL020; 35 nights, adults				
N	287	--	277	284
N (%) with prespecified abnormal change in QTc	6 (2.1%)	--	8 (2.9%)	9(3%)
Difference from placebo			0.8%	1.1%
95% C.I. of Difference			-2.0 , 3.7	-1.7 , 4.0
TL025; 35 nights, elderly				
N	274	281	274	--
N (%) with prespecified abnormal change in QTc	11 (4.0%)	10 (3.6%)	8 (2.9%)	--
Difference from placebo		-0.5%	-1.1%	--
95% C.I. of Difference		-3.9 , 2.9	-4.4 , 2.2	
TL021; 35 nights, adults				
N	131	--	139	135
N (%) with prespecified abnormal change in QTc	1 (0.8%)	--	4 (2.9%)	11 (8.1%)
Difference from placebo		--	2.1%	7.4%
95% C.I. of Difference			-1.7 , 6.4	2.5 , 13.3

Endocrine system
Evidence from the literature suggests that melatonin affects the endocrine system. Decline in testosterone and increase in prolactin were also seen in one phase 1 trial. Therefore, effects on the endocrine system were assessed in several clinical studies.

The results of these studies indicated that ramelteon did not appear to affect the thyroid or adrenal axes. Furthermore, results indicated that, ramelteon did not adversely impact the therapeutic effects of levothyroxine.

However, an elevation in mean serum prolactin was seen in subjects receiving ramelteon. These results were driven by observations in women.
Examination of the prolactin values for individual subjects in both treatment groups revealed that a total of 12 of 65 (18.5%) subjects in the placebo group and 16 of 57 (28.1%) subjects in the ramelteon group had prolactin levels within the reference range at Baseline that increased to above the reference range at some point during the treatment period. These increases were reported as AEs for 6 of the ramelteon-treated subjects and for none of the placebo-treated subjects although these were asymptomatic. The prolactin levels for 5 of the 6 subjects, for whom increased prolactin AEs were reported normalized over time.

- Safety in special populations

Age gender, race and body mass index
AEs stratified according to age categories are presented in table 16 below. The AEs pattern in the elderly and very elderly subjects was essentially similar to that seen in the total population, except for dysgeusia, myalgia, and depression, which in the elderly were more frequent in the active groups compared to placebo (see table below).

Table 16 AEs by Age in ≥2% of Subjects

Variable	Placebo (n=1233)	Ramelteon 4 mg (n=486)	Ramelteon 8 mg (n=1177)	Ramelteon 16 mg (n =585)	Ramelteon 32 mg (n=105)	Ramelteon All Doses (n=1937)
< 40 Years of Age	**(n = 398)**	**(n = 61)**	**(n = 347)**	**(n = 270)**	**(n = 61)**	**(n = 281)**
Subjects with any event	172 (43.2)	16 (26.2)	146 (42.1)	131 (48.5)	14 (23.0)	281 (50.5)
Headache	41 (10.3)	5 (8.2)	36 (10.4)	33 (12.2)	5 (8.2)	74 (13.3)
Somnolence	15 (3.8)	0	19 (5.5)	23 (8.5)	0	42 (7.6)
Nausea	8 (2.0)	2 (3.3)	15 (14.3)	8 (3.0)	0	24 (4.3)
Nasopharyngitis	20 (5.0)	0	12 (3.5)	10 (3.7)	0	22 (4.0)
Fatigue	6 (1.5)	0	11 (3.2)	7 (2.6)	1 (1.6)	19 (3.4)
Pharyngitis	9 (2.3)	2 (3.3)	9 (2.6)	6 (2.2)	3 (4.9)	19 (3.4)
Dizziness	11 (2.8)	0	12 (3.5)	3 (1.1)	0	15 (2.7)
Insomnia	7 (1.8)	0	5 (1.4)	7 (2.6)	0	12 (2.2)
Dyspepsia	2 (0.5)	0	3 (0.9)	6 (2.2)	2 (3.3)	11 (2.0)
40 - <65 Years of Age	**(n = 462)**	**(n = 45)**	**(n = 456)**	**(n = 315)**	**(n = 44)**	**(n = 727)**
Subjects with any event	190 (41.2)	7 (15.6)	165 (36.2)	157 (49.8)	7 (15.9)	321 (44.2)
Headache	29 (6.3)	1 (2.2)	37 (8.1)	30 (9.5)	1 (2.3)	68 (9.4)
Insomnia	9 (1.9)	0	17 (3.7)	17 (5.4)	0	34 (4.7)
Somnolence	9 (1.9)	0	12 (2.6)	18 (5.7)	2 (4.5)	31 (4.3)
Fatigue	11 (2.4)	0	17 (3.7)	11 (3.5)	1 (2.3)	28 (3.9)
Nausea	12 (2.6)	1 (2.2)	7 (1.5)	14 (4.4)	1 (2.3)	23 (3.2)
Upper Respiratory tract infection	7 (1.5)	1 (2.2)	14 (3.1)	4 (1.3)	0	19 (2.6)
Dizziness	11 (2.4)	0	9 (2.0)	8 (2.5)	0	17 (2.3)
Nasopharyngitis	14 (3.0)	0	5 (1.1)	9 (2.9)	1 (2.3)	15 (2.1)
65 - <75 Years of Age	**(n = 261)**	**(n = 272)**	**(n = 261)**	**(n = 0)**	**(n = 0)**	**(n = 455)**
Subjects with any event	103 (39.5)	112 (41.2)	109 (41.8)	0	0	217 (47.7)
Dizziness	11 (4.2)	11 (4.0)	13 (5.0)	0	0	24 (5.3)
Headache	11 (4.2)	10 (3.7)	14 (5.4)	0	0	23 (5.1)
Myalgia	3 (1.1)	10 (3.7)	12 (4.6)	0	0	22 (4.8)
Dysgeusia	6 (2.3)	6 (2.2)	14 (5.4)	0	0	20 (4.4)
Somnolence	3 (1.1)	9 (3.3)	7 (2.7)	0	0	16 (3.5)
Depression	2 (0.8)	6 (2.2)	9 (3.4)	0	0	15 (3.3)
Insomnia	8 (3.1)	4 (1.5)	9 (3.4)	0	0	13 (2.9)
Nasopharyngitis	2 (0.8)	7 (2.6)	6 (2.3)	0	0	13 (2.9)
Nausea	6 (2.3)	7 (2.6)	7 (2.7)	0	0	12 (2.6)
Eye pain	2 (0.8)	7 (2.6)	4 (1.5)	0	0	11 (2.4)
Fatigue	6 (2.3)	4 (1.5)	6 (2.3)	0	0	10 (2.2)
Decreased appetite	1 (0.4)	6 (2.2)	3 (1.1)	0	0	9 (2.0)
Muscle twitching	2 (0.8)	5 (1.8)	4 (1.5)	0	0	9 (2.0)
Paraesthesia	3 (1.1)	5 (1.8)	4 (1.5)	0	0	9 (2.0)
Pruritis	2 (0.8)	7 (2.6)	2 (0.8)	0	0	9 (2.0)
≥75 Years of Age	**(n = 112)**	**(n = 108)**	**(n = 113)**	**(n = 0)**	**(n = 0)**	**(n = 199)**
Subjects with any event	41 (36.6)	52 (48.1)	55 (48.7)	0	0	107 (53.8)
Dizziness	7 (6.3)	10 (9.3)	11 (9.7)	0	0	21 (10.6)
Headache	3 (2.7)	6 (5.6)	5 (4.4)	0	0	11 (5.5)
Myalgia	3 (2.7)	5 (4.6)	5 (4.4)	0	0	10 (5.0)
Fatigue	2 (1.8)	2 (1.9)	6 (5.3)	0	0	8 (4.0)
Somnolence	2 (1.8)	3 (2.8)	5 (4.4)	0	0	8 (4.0)
Depression	1 (0.9)	5 (4.6)	2 (1.8)	0	0	7 (3.5)
Dysgeusia	3 (2.7)	2 (1.9)	5 (4.4)	0	0	7 (3.5)
Eye pain	4 (3.6)	4 (3.7)	3 (2.7)	0	0	7 (3.5)
Diarrhea	3 (2.7)	2 (1.9)	4 (3.5)	0	0	6 (3.0)
Dry mouth	1 (0.9)	1 (0.9)	5 (4.4)	0	0	6 (3.0)
Insomnia	1 (1.8)	3 (2.8)	3 (2.7)	0	0	6 (3.0)

Pruritis	3 (2.7)	1 (0.9)	4 (3.5)	0	0	5 (2.5)
Asthenia	2 (1.8)	2 (1.9)	2 (1.8)	0	0	4 (2.0)
Decreased appetite	0	1 (0.9)	3 (2.7)	0	0	4 (2.0)
Lethargy	0	2 (1.9)	2 (1.9)	0	0	4 (2.0)
Muscle twitching	1 (0.9)	3 (2.8)	1 (0.9)	0	0	4 (2.0)
Urinary tract infection	2 (1.8)	1 (0.9)	3 (2.7)	0	0	4 (2.0)

No clinically meaningful differences were detected with regard to gender, race or body mass index.

Hepatic impairment; renal impairment, COPD, and sleep apnea
As the liver is the major route of ramelteon metabolism, the impact of hepatic dysfunction on the pharmacokinetics of ramelteon was evaluated. Ramelteon 16 mg was administered to 24 subjects who had a clinical diagnosis of liver cirrhosis with either mild or moderate hepatic impairment as defined by the Child-Pugh classification system. The controls were 24 healthy subjects who were matched to cases by age, gender, race, weight and smoking status.

The kinetic results indicate that exposure is increased 8 to 10 fold with respect to AUC and 6 to 8 fold with respect to Cmax in patients with moderate impairment.

A summary of the AEs reported in this study is provided in table 17 below. No treatment-related effect was apparent, as incidences of events were generally similar between the matched groups. No clinically meaningful changes in physical examination findings, ECG findings, or vital signs were reported in this study. No laboratory values were reported as AEs.

Subjects with severe hepatic impairment were not studied, and the use of ramelteon by such subjects is not recommended.

Table 17 AEs experienced by 2 or More Subjects in hepatic impairment study

	Hepatic Impairment		**Hepatic Impairment**	
SOC	**Healthy Matched**		**Healthy Matched to Moderate**	**Moderate**
Preferred Term	**to Mild (n=12)**	**Mild (n=12)**	**(n=12)**	**(n=12)**
Any AE n (%)	9 (75)	10 (83)	10 (83)	9 (75)
Nausea	0	0	0	2 (17)
Lethargy	1 (8)	0	1 (8)	3 (25)
Headache NOS	2 (17)	2 (17)	2 (17)	2 (17)
Somnolence	6 (50)	8 (67)	9 (75)	7 (58)

In a similarly designed study which included subjects with varying degrees of renal impairment (mild, moderate, severe, and those requiring hemodialysis) and matched controls ramelteon exposure did not change markedly in subjects with mild or moderate renal impairment or subjects who require chronic hemodialysis compared to the healthy matched controls. Approximately 4-fold and 2-fold increases in the ramelteon area under the concentration-time curve (AUC) were observed in subjects with severe renal impairment on Day 1 and after 5 days of dosing, respectively, compared with the corresponding healthy subjects. The 4-fold mean increase on Day 1 was primarily due to an increase in 1 subject.

A summary of the AEs reported in this study is provided in table 18 below. A greater proportion of subjects reported AEs in the renal impairment group than their healthy counterparts (76% compared with 57%); however, many subjects with renal impairment had preexisting medical conditions.

One subject with severe renal impairment had a SAE (myocardial infarction) 28 days after the last dose, and 1 subject with severe renal impairment discontinued participation due to an AE (bronchitis and acute respiratory infection); neither event was considered related to the study drug. One healthy subject (with a known history of 1st degree AV block) had an ECG finding of multiple ventricular premature complexes that was detected 2 days after the last dose of study drug and reported as an AE.

Table 18 AEs experienced by 2 or More Subjects in renal impairment study

		Renal Impairment				
SOC Preferred Term	**Healthy Subjects (n=21)**	**Mild (n=8)**	**Moderate (n=5)**	**Severe (n=7)**	**Subjects on Hemodialysis (n=9)**	**All Subjects With Renal Impairment (n=29)**
Any AE n (%)	12 (57)	6 (75)	4 (80)	5 (71)	7 (78)	22 (76)
Somnolence	3 (14)	4 (50)	1 (20)	2 (29)	0	7 (24)
Headache NOS	3 (14)	0	2 (40)	1 (14)	1 (11)	4 (14)
Venipuncture site bruise	3 (14)	2 (25)	1 (20)	0	0	3 (10)
Ecchymosis	1 (5)	2 (25)	0	1 (14)	0	3 (10)
Dizziness	0	2 (25)	0	0	0	2 (7)
Dermatitis contact	2 (10)	0	0	0	0	0
Muscle cramps	2 (10)	0	0	0	0	0

A double-blind, placebo-controlled, 2-period crossover study was carried out in 26 subjects with obstructive sleep apnea who received ramelteon 16 mg or placebo for 1 night. There were no significant effects of ramelteon compared to placebo in the apnea/hypopnea indices, the number of central apneas per hour of sleep, number of mixed apneas per hour of sleep, number of obstructive apneas per hour of sleep, and mean arterial oxygen saturation during sleep and for each stage of sleep. Three subjects reported AEs in the sleep apnea study, all after receiving ramelteon: 2 subjects reported headache and 1 subject reported a urinary tract infection. Single doses of ramelteon 16 mg did not exacerbate sleep apnea or apnoea-related hypoxemia in subjects with mild to moderate obstructive sleep apnoea.

A similarly designed crossover study was carried out in 26 subjects with chronic obstructive pulmonary disease. Treatment with ramelteon showed no significant differences from placebo in mean arterial oxygen saturation during sleep for the entire night, for each stage of sleep, or for each hour of sleep, and no significant difference in the apnea/hypopnea index. The ramelteon group had significantly longer mean total sleep time than the placebo group (380.6 vs 353.6 minutes; P=0.015). One subject had an AE of increased triglycerides after receiving ramelteon. Another subject had an increase in QTc of at least 30 milliseconds after treatment with both placebo and ramelteon. No other clinically meaningful changes in physical examination findings, ECG findings, clinical laboratory values, or vital signs were reported in this study.

- Safety related to drug-drug interactions and other interactions

In vitro studies show that ramelteon is metabolised via cytochrome P-450 (CYP) 1A2, and to a minor extent via the CYP2C subfamily and CYP3A4. When ramelteon 16 mg was co-administered with fluvoxamine (a potent CYP1A2 inhibitor) plasma concentration of ramelteon was increased 190-fold.

However, the safety profile of ramelteon was not adversely affected. Such an increase in concentration was not seen with fluoxetine.
In the clinical trials program, subjects were taking a number of commonly prescribed medications and no individual drugs or classes of drug were identified as having any influence on the reported safety profile.

Two studies were conducted to assess the interaction of ramelteon and alcohol. In subjects receiving alcohol and ramelteon together, an effect was seen on psychomotor performance, although effects were not consistent across all measures.

- Post marketing experience

The International Birth Date (IBD) of ramelteon was designated as 22 July 2005, which is the date of the first marketing authorisation for the product in the US. The product has been approved and marketed (as of 21 January 2006) in the US only. The applicant has submitted the two half-yearly PSURs that have been prepared since the IBD (and submitted to the FDA) together with the application. The first PSUR covered the period 22 July 2005 through 21 January 2006 and the second PSUR the period 22 January 2006 through 21 July 2006.
The first version of the Company Core Data Sheet (CCDS), dated January 2006, which includes the Reference Safety Information (RSI), was appended to the PSURs. No changes to the RSI were made during both periods under review.

Patient exposure
Cumulative market patient exposure for ramelteon for the entire reporting period was approximately 489,000 patients in the US (first period: 144,000 patients; second period 345,000 patients).

Adverse reactions
The number of cases reported for both periods under review are presented in the table below:

Table 19: Number of cases reported per PSUR period divided by seriousness and listedness

	# Cases PSUR 1	**# Cases PSUR 2**	**Total**
Serious unlisted cases	9	11 (2 fatal)	**20**
Serious listed cases	0	1	**1**
Total serious cases	9	12	**21**
Non-serious unlisted cases	107	119	**126**
Non-serious listed cases	39	13	**52**
Total non-serious cases	146	132	**278**
Grand total cases	**155**	**144**	**299**

Fatal cases
As can be seen in the table, the applicant retrieved 21 serious unlisted cases during the period under review of which 2 had a fatal outcome. In the first case a 30-year-old female patient died of unknown cause; an autopsy was performed, but the results were not obtained. The case was very poorly documented. The second case involved an 80-year-old male patient under hospice care for a concurrent end-stage bladder cancer who experienced myocardial infarction, chest pain, anaemia and metabolic acidosis while on ramelteon. He had a medical history of among others COPD, repaired triple abdominal aneurysm, renal insufficiency and elevated cholesterol.
The 115 cases reported during PSUR #1 reflected 225 adverse reactions; the 144 cases reported during PSUR #2 reflected 249 adverse reactions, which add up to a total of 474 adverse reactions reported for the entire period under review.

Adverse reactions were most frequently reported involving the SOCs Psychiatric disorders (112 adverse reactions), Nervous system disorders (96) and General disorders and administration site conditions (84). The most frequently reported reactions were: drug ineffective (33 times reported), somnolence (26) and nightmare (22, unlisted). Frequently reported reactions (≥ 4 times reported) are summarised in the following table.

Table 20: Frequently reported adverse reactions (≥ 4 time reported) for the entire period under review

Adverse reaction	Frequency	Adverse reaction	Frequency
Drug ineffective*	33	Feeling abnormal*	7
Somnolence	26	Poor quality sleep*	6
Nightmare*	22	Palpitations*	6
Abnormal dreams*	17	Vomiting*	6
Insomnia*	17	Drug interaction*	6
Dizziness	17	Heart rate increased*	6
Headache	13	Excitability*	5
Middle insomnia*	13	Drug dispensing error*	5
Anxiety*	11	Migraine*	4
Initial insomnia*	11	Sedation*	4
Hallucination*	10	Restless legs syndrome*	4
Agitation*	9	Rash*	4
Nausea	8	Fatigue	4
Overdose*	8	Hangover*	4
Hypersomnia*	7	Prescribed overdose*	4

* means the reaction is unlisted

Cases of interest

Anaphylactic reactions/ hypersensitivity

In total two serious cases of anaphylactic reactions and two serious cases of hypersensitivity were retrieved by the applicant during the entire period under review. In three of the cases the events were probably related to ramelteon in view of the temporal relationship and in the fourth case possibly related. The applicant will include anaphylactic reaction as an adverse reaction to the RSI.

Hallucinations

A total of 12 cases of hallucinations of which one was serious were retrieved by the applicant during the entire period under review. In the serious case a 72-year-old male patient who found ramelteon 8 mg ineffective after taking it for 2 nights. He took a 16 mg dose, experienced hallucinations and was hospitalised. Ramelteon was discontinued and the patient recovered. In four other cases there was a positive dechallenge. The remaining 7 cases were lacking outcome information. The applicant outside the PSURs reports on one other serious case of hallucinations/paranoia/abnormal behaviour in a 47-year-old female patient with positive dechallenge. Eight of the 13 cases did not report type of hallucinations, 2 cases reported visual hallucinations, 2 reported mixed hallucinations and one case reported 'felt like tripping on acid'. Auditory hallucinations have not bee reported.

The reports retrieved during the post-marketing period confirm the findings from the clinical trials. Hallucinations should be classified as adverse reactions.

Convulsions/ loss of consciousness

The applicant retrieved two cases of convulsions and one of loss of consciousness (all serious) during the period under review, all during the period of PSUR #1. During the period of PSUR #2 one non-serious case of muscle spasms was reported.

The cases were:

A female patient of unknown age, with a history of insomnia and substance abuse experienced blacking out after receiving treatment with ramelteon for an unknown period of time. A 19-year-olfd female patient with ADHD and on an unspecified stimulant, experienced seizures while on ramelteon for about 10 days. Outcome was not reported. The reporting physician assessed the seizures as definitely related to ramelteon since no other therapy was added. A 66-year-old male patient experienced a seizure while sleeping after using ramelteon. The seizures did not recur after discontinuation of ramelteon.

Cardiac disorders
The applicant retrieved four serious cardiac cases during the entire period under review of which one had a fatal outcome and is described above.

A 72-year-old male patient with a history of atrial fibrillation experienced a breakthrough of atrial fibrillation on the fifth day of treatment with ramelteon at bedtime. Ramelteon was discontinued at the sixth day and the events resolved. Concomitant medication included amiodarone, warfarin, atenolol and levothyroxine.
A 69-year-old female patient experienced dizziness, nausea, vomiting, elevated BUN and bradycardia coincident with ramelteon. Ramelteon was discontinued and heart rate returned to 60.
A 43-year-old female patient experienced chest pain approximately 2 hours after taking ramelteon, which awoke her from her sleep. The pain radiated to her jaw, shoulder and arm and she felt cold and clammy. In the ambulance the patient was informed to have an elongated QRS complex. Upon arrival in the ER her cardiac monitor showed normal sinus rhythm with increased pulse rate and BP. Her EKG, stress test, cardiogram and cardiac enzymes were normal. Ramelteon was discontinued and the events have not recurred.

In addition, a total of ten non-serious cases of palpitations were reported during the entire period under review. In the majority of patients time onset was short and some had a positive dechallenge.
In two cases of palpitations a drug interaction with levothyroxine was co-suspected. In both cases the palpitations resolved when ramelteon was stopped. The applicant notes that a review of the 93 patients also on levothyroxine in a US 12 month open-label safety study of ramelteon did not reveal any clinically significant effects upon the thyroid axis.

Sleep paralysis
The applicant retrieved two serious cases of sleep paralysis. One case was poorly documented and in the other abnormal dreaming was co-reported. The events in this case led to discontinuation of ramelteon. In addition, a case in which a male patient felt paralysed after just one dose of ramelteon, and the next day he felt sluggish was reported. In this latter case outcome of discontinuation of ramelteon was unknown.

Prolactin increased/ galactorrhoea
The applicant retrieved one case of galactorrhoea and two non-serious cases of blood prolactin increased during the period under review. The applicant also retrieved a serious case of breast enlargement, galactorrhoea and blood prolactin abnormal after one week of ramelteon use with positive dechallenge and rechallenge. A warning on the issue is included in the proposed ramelteon SPC. The RSI notes 32% of all patients which were treated with ramelteon in a placebo-controlled clinical trial evaluating among others the reproductive axis had prolactin levels increased, mostly women, compared to 19% in the placebo group.

Miscellaneous
Nightmares, abnormal dreams, anxiety and agitation belong to the most frequently reported non-serious adverse reactions (see table 20 above) and are not included in the proposed SPC. Anxiety and agitation were often co-reported with palpitations and nightmares.
In addition, single serious cases of acute pancreatitis after one week of treatment with positive dechallenge, sleep walking resulting in a fall down the stairs and vaginal haemorrhage with positive de-and rechallenge were retrieved by the applicant.

Lack of efficacy
During the period of PSUR #1 there were 17 cases of ‘drug ineffective’ and in total 42 cases representing lack of efficacy (for instance ‘therapeutic response decreased’ and ‘insomnia’ also counted in), which corresponds with 27% of all cases reported and a reporting rate of 0.03% (number of cases divided by patient exposure). During the phase I through III clinical trials lack of efficacy was reported in 2.9% of placebo-treated patients (n = 1151) compared with 7.0% or ramelteon-treated patients (n = 3493).
A possible reason for the high number of lack of efficacy reports may be channelling bias (those patients that do not react to other insomnia treatments tend to divert to the new product for this

indication). During the period of PSUR #2 there were 16 drug ineffective cases and in total 32 cases representing lack of efficacy, which corresponds to 22% of all cases reported for that period and a reporting rate of 0.01%. It seems that the rate of lack of efficacy reporting is declining.

Drug interactions
A total of six non-serious interaction cases were retrieved by the applicant during the entire period under review. Two of the cases involved a possible interaction with levothyroxine and resulted in palpitations and anxiety. The remaining four interaction cases were all singly reported and involved: drug interaction with quetiapine resulting in drug ineffective, drug interaction with fluoxetine resulting in nasal dryness (positive dechallenge), interaction with alprazolam resulting in sedation and drowsiness lasting the entire next day, interaction with fluconazole resulting in ageusia.

Overdose
The applicant retrieved nine cases of overdose (over 8 mg daily) during the period under review. Five of the nine cases reported a lack of efficacy, and in one case no adverse reaction was reported. The three remaining cases reported hallucinations (at 16 mg), middle insomnia and abnormal thinking (at 8 mg) and tremors (at 24 mg).

The applicant states to have retrieved a total of 70 overdose cases reported by healthcare professionals and consumers during the first 18 months of marketing in the US. With exception of two cases no case exceeded 24 mg. A 66-year-old female patient took approximately 90 tablets of ramelteon within 5 hours to commit suicide, which made her slightly drowsy but oriented and did not require treatment. A 41-year-old female patient intentionally took 30 ramelteon tablets and up to 60 alprazolam (0.5 mg) and was in a coma for several days.

Drugs abuse/misuse
There were no cases of drug abuse or misuse reported during the periods under review

- Discussion on clinical safety

The safety of ramelteon has been studied in approximately 6,000 subjects who participated in the development program of this substance. The numbers of patients exposed for long and short duration and in the elderly are in accordance with regulatory standards as specified in ICH-E1 and E7. There is only limited information on exposure of elderly patients (≥65 years), particularly the very elderly (≥75 years), to doses over 8 mg ramelteon. As the indicated dose for adults and elderly is 4 to 8 mg, this is not a problem in normal use, but overdose information is limited to the adult population and not available for the elderly.
There were several AEs, specifically in the area of neurological and psychiatric symptoms that occurred more frequently in ramelteon treated subjects compared to placebo. These included memory impairment, lethargy, sedation and balance, as well as depression, anxiety, derealization, abnormal dreams, restlessness, agitation, disorientation, emotional disorder, hallucination, mental disorder, and stress. The causal mechanism responsible for these events is unclear, and the increase in some of these events, raise reason for some concern.
The risk of depression AEs is specifically high in the elderly (aged > 65) where more then 40 events per 100 patient years were observed in the Ramelteon treated groups compared to 9 in placebo. In patients younger than 65 these figures were 8.4 vs. 4.1 per 100 patient year for Ramelteon vs. placebo respectively, which constitute a considerable risk as well. The risk represented by this increased rate of depression, especially in the elderly, does not seem to be justified, especially at the face of the weak efficacy results.

In addition, it is noted that the elderly in general are more sensitive for adverse events in the area of neurological and psychiatric symptoms.

Serious AEs and Death
Three deaths and several serious AEs (SAEs) occurred during the studies. The three deaths included two subjects who died following motor vehicle accidents in which they were involved as pedestrians. The third was death by suicide in a placebo arm.

The applicant makes a convincing case in arguing that the two fatal accidents are not related to Ramelteon. Further, examination of traffic accidents in the clinical trial database indicates that higher rates are found in placebo, which, again, argues against a causal relationship with Ramelteon. The rate of these events in the open label study (0.4%) is somewhat higher but this can be ascribed to the longer period of exposure compared to the controlled studies.

Further 24 serious AEs occurred in the controlled studies that included subjects with insomnia, 15 (0.8%) in ramelteon treated subjects and 9 (0.7%) in placebo. Additional SAEs occurred in the open label 12 month study. Several of these events were considered possibly related to study drug. These included: a transient Ischemic attack, paranoid schizophrenia, cerebrovascular accident, prolactinoma, and syncope. With such small numbers in each category, it is difficult to estimate causality of these events.

QT
With respect to QTc prolongation the results appear mixed, in the elderly study a higher percentage of subjects in the placebo treated group had abnormal changes in QTc compared to subjects in the active group. However, in the two adults studies the results were in the opposite direction, with one 16 mg group showing a higher proportion of subjects with abnormal QTc changes (8.1%) compared to placebo (0.8%). A QTc concern cannot be excluded.

Hormonal changes
Results of the laboratory tests indicate an association of treatment with increase in prolactin and other hormone levels. There was one report of galactorrhoea. Hormonal changes are of lesser concern if indeed treatment is limited to short-term duration (i.e. 5 weeks). Nevertheless, if the product was approved, such changes and associated risks (e.g. galactorrhoea, osteoporosis) should have been mentioned in the SPC and should be monitored postmarketing. Hyperprolactinaemia and associated risks (e.g. gynaecomastia, breastcarcinoma, fertility) would be a problem if treatment were to continue off-label for a longer duration.

Hepatic impairment; renal impairment, COPD, and sleep apnea
Although no signals were detected among subjects with hepatic or renal impairment, COPD, or sleep apnea, the extent of exposure in the different studies does not allow accurate conclusions.

Interactions
Ramelteon is metabolised via cytochrome P-450 (CYP) 1A2, and to a minor extent via the CYP2C subfamily and CYP3A4, caution is called for when co-administering drugs that claim the same systems. One such instance is fluvoxamine (a potent CYP1A2 inhibitor) which showed an increased plasma concentration of 190 fold when co-administered with ramelteon. The fact that the safety profile of ramelteon did not seem to be adversely affected may indicate that there is no pharmacodynamic effect of importance.

Dynamic interactions with benzodiazepines have not been examined in the research program of Ramelteon. The MAA indicates that it is conceivable that the combined administration of ramelteon and a benzodiazepine could create an enhanced pharmacodynamic effect, particularly as an additive effect on sleep or a prolongation of somnolence, which could impact driving ability and/or cognitive function.
The MAA proposed to add a section in the RMP about this issue. In addition, the potential for a dynamic interaction should be studied systematically. Co-administration of additional treatments (e.g. benzodiazepines) together with Ramelteon is likely; as these other treatments may be necessary to address additional sleep components (if the indication of Ramelteon is limited to improving only sleep latency).

Effects on Balance and next day functioning (driving)
Several safety issues are of special interest due to their known connection with existing sleep medication, including effects on balance, abuse potential, next morning effects on driving and concentration.

The effect on balance was examined in a paradigm where subjects were woken up several hours following bedtime dosing. In this paradigm ramelteon had a similar effect to that of placebo and fared better than the active comparators zopiclone and zolpidem. However, the absence of an adverse effect of Ramelteon on balance might be due to lack of efficacy.

Next morning effect on driving ability showed statistically significant deviation (2.2 cm) that was only slightly smaller compared to zopiclone (2.9 cm). Additional next-morning effects were seen including increase in reaction time, delayed word recall test and decreased attention and motor control. These effects, strengthen the concern regarding the potential effect of ramelteon on functioning in the next day. The SPC warning regarding driving adequately addresses this risk (i.e. Ramelteon has an minor influence on the ability to drive or use machines the morning after therapy. Patients should be advised not to drive or operate machinery the morning after treatment until it is established that their performance is unimpaired.)

Abuse potential

Abuse liability seems not to be of any concern with respect to ramelteon. This was demonstrated in two studies with triazolam as active comparator and placebo.

Withdrawal and rebound

Derealization, abnormal dreams, and nightmares are typical withdrawal symptoms from benzodiazepines. The applicant was asked to indicate whether these events occurred during the single-blind run-out period or in the beginning of treatment in order to assess whether these reflected withdrawal phenomena. An evaluation of the ramelteon clinical development database revealed that no new onset events of these AEs occurred during the single-blind run-out periods of any study.

In the context of safety in comparison with available sleep medication, withdrawal and rebound were evaluated in some of the efficacy studies in the period following double blind treatment. Although these studies would seem to suggest that withdrawal and rebound did not occur, these studies did not include active control and therefore cannot be unambiguously interpreted. A lack of an effect on withdrawal or rebound might be due to lack of assay sensitivity of the studies. In addition, the questionnaire used to assess withdrawal symptoms (the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)) captured symptoms that are typical for benzodiazepine withdrawal while potential withdrawal symptoms from ramelteon are not necessarily identical to those encountered with benzodiazepine and would therefore not be adequately assessed by a benzodiazepine specific instrument. In addition, one cannot exclude that rebound insomnia can occur after a longer period from the time of treatment cessation, because it is not known what the biological half-life for the effects of Ramelteon is. The applicant was asked to conduct a study with an adequate duration of assessment after treatment cessation, with an appropriate control, and an appropriate scales to assess withdrawal and rebound.

The response of the applicant to these concerns was that there is no validated instrument to assess withdrawal and rebound potential of a selective melatonin agonist. Furthermore, although the biological half-life of Ramelteon is not known, it was suggested that it is similar to its pharmacokinetic half-life and that it is therefore reasonable to evaluate rebound and withdrawal on the same time schedule as for GABAergic compounds with a short half-life. This response does not address the issue of potential for withdrawal symptoms after a longer period of time e.g. after the potential chronobiotic effect has elapsed and does not provide any evidence to support a contention of biological half life which is similar to kinetic half life. In addition, the potential lack of assay sensitivity of the studies, i.e. the sensitivity to detect withdrawal symptoms, which cannot be determined due to the lack of an active control arm, was not addressed.

Nevertheless, given the conclusion that the product lacks efficacy, withdrawal and rebound are not expected.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfilled the legislative requirements

Risk Management Plan

The MAA submitted a risk management plan

The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Ramelteon film-coated tablets are manufactured and controlled in a satisfactory way, and the product should perform consistently well in the clinic, from batch to batch. There are no unresolved quality issues that could have an impact on the benefit/risk balance.

Discussion on the non-clinical aspects

Pharmacology
Ramelteon is a specific agonist of the melatonin MT1 and MT2 receptor. The sleep-promoting action consisted mainly in the reduction of sleep-latency. The pattern of the effects was clearly different from that of benzodiazepine-like compounds.
An important shortcoming of the dossier is the lack of data on the pharmacological effect of repeated administration since it can be expected that repeated administration will result in an adaptation of the effect.
The secondary pharmacodynamic data support the high selectivity of the product. However, with respect to the effect on hormones subject to a daily rhythm the dossier is very limited.
The safety pharmacology data suggest a pharmacodynamic interaction with barbiturates, but other data with benzodiazepines do not support a pharmacodynamic interaction with respect to sedative effects. Ramelteon is not expected to interfere with the cardiovascular, the respiratory, and the gastrointestinal and renal systems.

Pharmacokinetics
Ramelteon showed a quick and high intestinal absorption; however, it is subject to high first-pass metabolism resulting in a low bioavailability.
At lower doses repeated administration leads to increasing exposure, indicating accumulation. At higher doses repeated dosing results in decreasing exposure, indicating increased biotransformation due to enzyme induction.

After single dose, ramelteon rapidly distributed over the body, penetrating well in brain tissues. After repeat oral administration the highest concentrations were found in thyroid gland, lungs, spleen, kidneys, skin, fat tissue, and femur. It passes the placenta and is found in the breast milk.

Under *in vitro* conditions, CYP1A2 metabolises ramelteon to the most important human metabolite M2, which mainly consists of the 2S, 8S form.

Ramelteon is mainly excreted in urine.

Studies on metabolite profiles after a dose of radiolabelled ramelteon show that the sum of the concentrations of the identified metabolites in plasma, brain, urine, faeces and bile constitutes only a small portion of the total radioactivity found in these matrices. A major part of the radioactivity is present in the form of other, unidentified, metabolites. As this could be due to the diversion of the labelled propionamide moiety, the fate of the remaining part of the ramelteon molecule has not been documented.

Results from interaction studies showed that the effect of CYP1A2 inhibitors such as fluvoxamine resulted in a very large increase of ramelteon exposure (AUC increased more than 190 fold), but an insignificant effect on M2 levels. These results were confirmed in humans.

Toxicology
Ramelteon was well tolerated by rats and monkeys when administered as a single dose of up to 2000 mg/kg/day. The acute toxicity is low. Lethal doses after oral administration were between 600-2000 mg/kg/day for rats and higher than 2000 mg/kg/day for monkeys.

In studies on repeat dose toxicity of ramelteon, decreased locomotor activity and emesis were observed. Body temperature and heart rate were decreased in monkeys in one study.
At high doses decreases in food consumption and body weight occurred; convulsions occurred infrequently.

Liver adaptations: in mice and rats, high doses of ramelteon resulted in increased liver weight, enlarged liver, hepatocellular hypertrophy and increased liver enzymes and cholesterol. These adaptive liver responses may have led to changes observed in the thyroid gland and levels of thyroid hormones.

Other organs: enlarged or increased weights of the adrenal gland and decreased thymus weight were observed at high doses indicating no likely safety concern for humans.

Ramelteon is not *genotoxic*, although one *in vivo* chromosomal aberration test showed equivocal results, which could not be explained by cytotoxicity. The evidence is sufficient to conclude that there is no genotoxic potential, due to the negative *in vivo* results.

Three types of tumour with increased incidence after treatment with ramelteon are Harderian gland adenomas in mice, liver tumours in mice and rats, and Leydig cell tumours in the testis of rats. The increase in hepatic tumours coincided partly with an increase in hepatic enzymes, which is a known cause of carcinogenicity in rodents but not in humans. As Harderian gland does not exist in humans and the safety margins were in general very high, the *carcinogenic* potential of ramelteon is not of concern in humans.

Even though toxicology studies did not indicate *reproductive toxicity* concerns for humans, caution should still be exercised as the potential pharmacological modulation of hormones affecting pregnancy has not been investigated.

No ramelteon-related effects were evident in *local tolerance* studies.

Studies on the *dependence potential* revealed that ramelteon has a very low abuse liability and there is no evidence of withdrawal-related phenomena.

Efficacy
Altogether, it was concluded that short and long-term efficacy of Ramelteon in the treatment of primary insomnia was not demonstrated.

Specifically, evidence of efficacy focused on only one aspect – sleep latency - while efficacy concerning other aspects (i.e. sleep quality, number of awakenings, early morning awakening, next day functioning) was not demonstrated.

The applicant proposed to limit the indication to the treatment of sleep latency. However, only one of the three pivotal trials that were conducted in the natural setting resulted in statistical significant improvement in sleep latency. Additional trials that were conducted in the natural setting suffered from methodological shortcomings. Specifically, in one study (TL021) a large proportion of the initially screened patients were randomised although they didn't meet the inclusion criteria. Most importantly, the difference in sleep latency that was obtained in the trials was considered to be of doubtful clinical relevance.

In addition, long-term efficacy was not demonstrated, as the effect on latency diminished over time. This was due to increased improvement in the placebo arms while latency in the active arms remains constant resulting in a smaller difference.

Although a limited indication was approved for a benzodiazepine-like product, it is considered that the case of Ramelteon involves different considerations. Ramelteon is a new product with a different mechanism of action and therefore the data on efficacy cannot be supported by evidence from other benzodiazepine-like products.

In addition to the fact that minimal changes in sleep latency were observed, there are changes in sleep architecture showing an increase in light sleep at the expense of deep sleep. This is an unexpected result for a sleep medication, which has not been adequately explained.

Another weakness of this dossier is the fact that there was no adequate justification for the dose and no clear dose effect was shown across the clinical trials.

Safety

Altogether, the safety profile of Ramelteon raises some concerns. Specifically, the risk of depression AEs, was especially high in the elderly (aged > 65) where more then 40 events per 100 patient years were observed in the Ramelteon treated groups compared to 9 in placebo. In patients younger than 65 these figures were 8.4 vs. 4.1 per 100 patient year for Ramelteon vs. placebo, respectively, which constitute a considerable risk as well. The risk represented by the increased rate of depression weighs heavily against any potential benefit.

Altogether, with respect to the elderly, there is paucity of evidence regarding exposure to higher doses and to overdose.

Other AEs that were encountered in the clinical studies as well as post-marketing included neurological, psychiatric, and cardiovascular events. The risk of cardiovascular problems could be of concern taking into account that a large portion of potentially exposed patients would be elderly.

Hormonal changes, including decreased testosterone, hyperprolactemia, and galactorrhoea raised additional concerns. If treatment would indeed be limited to short-term duration (i.e. 5 weeks) this would be of less concern.

Risk-benefit assessment

The evidence in the Ramelteon dossier indicates that only one aspect of sleep was examined: sleep latency. The applicant proposed to limit the indication to only this aspect, therefore applying for the "*treatment of primary insomnia characterised by difficulty falling asleep in patients 18 years and older"*. However, even if targeting of individual symptom within a syndrome would have been possible, the effect was not observed consistently.

In one of the three pivotal studies conducted in the natural setting (TL 025), more than 270 patients were enrolled for each of the three arms, placebo, ramelteon 4 and 8 mg. A statistically significant effect was demonstrated at week 1, with a difference from placebo of about 8 minutes and over a total time to sleep of about 78 minutes in the placebo arm and 70 minutes in the active arm. No effect dose relation was proven. In the other two studies, more than 270 patients (TL 020) and more than 370 patients (CCT002) entered each arm (ramelteon 16 mg was also administered), but no statistical significance was achieved for latency to sleep. Therefore the results obtained in the natural setting did not confirm the positive results of the laboratory studies.

The clinical relevance of the reduction in sleep latency that was found in the studies was considered insufficient. A reduction of 8 minutes in latency (in study TL025) is of doubtful clinical relevance, especially considering that it resulted from a reduction in latency from 78 minutes in the placebo treated subjects compared to latency of 70 minutes in the active group, hence proportionally a small improvement. Furthermore, the responders analyses that were carried out upon request of the CHMP (i.e. either <30 minutes sleep latency or >50% decrease from baseline) failed to show statistically significant differences between Ramelteon and placebo in the proportion of responders. The inclusion of an active control in the pivotal studies would have facilitated the interpretation of these data.
The conclusion from these results was therefore that efficacy was not demonstrated, the more so, as the effect was not supported by consistent effects in other areas of sleep.

In addition to lack of efficacy, the safety profile of Ramelteon raised a concern with respect to the risk of depression AEs, which were specifically high in the elderly (aged > 65) where more then 40 events per 100 patient years were observed in the Ramelteon treated groups compared to 9 in placebo. In patients younger than 65 these figures were 8.4 vs. 4.1 per 100 patient year for Ramelteon vs. placebo respectively, which constitute a considerable risk as well. The risk represented by this increased rate of depression, especially in the elderly, does not seem to be justified, especially at the face of the weak efficacy results. Additional safety issues include risk of cardiovascular events, risks associated with increased prolactin levels and uncertainty about dynamic interactions with benzodiazepines and other sleep medications.
The applicant gave an oral explanation before the CHMP addressing the concerns raised by the CHMP that the short- and long-term efficacy on primary insomnia or on sleep latency had not been demonstrated. The arguments brought forward by the applicant were that sleep latency, which meets the diagnostic criteria for insomnia, is an appropriate and important target for insomnia therapy and both objective and subjective assays are needed to assess this condition; that ramelteon demonstrated efficacy without risks associated with sedative properties of hypnotics. In addition, the applicant presented a new analysis with a composite subjective score (Z-score) which included subjective sleep latency, subjective total sleep time and sleep quality as parameters.
After the oral explanation and taking into account the additional comments from the applicant, the CHMP was still concerned by the lack of clinical relevance of the effect of ramelteon.

On the basis of all the above arguments, the CHMP considered that the benefit-risk balance for Ramelteon Takeda Global Research and Development Centre (Europe) LTD in the applied indication was negative, given that the short- and long-term efficacy on primary insomnia or on sleep latency had not been demonstrated.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus/ that the risk-benefit balance of Ramelteon Takeda Global Research and Development Centre (Europe) LTD 4 and 8 mg in the "*treatment of primary insomnia characterised by difficulty falling asleep in patients 18 years and older"* was unfavourable and therefore did not recommend the granting of the marketing authorisation.

Grounds for refusal

Whereas

1. Efficacy on sleep latency was not demonstrated. Only small differences between ramelteon and placebo arms were obtained. These effects were not consistently shown in the pivotal clinical trials and clinical relevance of these differences is doubtful.

2. No effect was seen on other sleep parameters, including no effects on next day functioning, so there is no support for the relevance of the effect from a clinical perspective.

3. Long-term efficacy was not demonstrated and a diminishing of the small effect obtained was seen even within the 5 weeks period that is proposed for treatment duration.