CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-782

MEDICAL REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

Addendum to Medical Officer Team Leader Memorandum

Date: July 22, 2005

To: File, NDA 21-782

From: Rigoberto Roca, M.D.
Deputy Director
Division of Anesthetic, Critical Care and Addiction Drug Products

Re: NDA 21-782: Ramelteon (TAK-375)
Takeda Global Research and Development, Inc.

This is an addendum to my Medical Officer Team Leader memorandum dated June 30th, 2005. It will articulate the reasons why I reached a different conclusion and recommendation from the primary clinical reviewer, Elizabeth McNeil, M.D.

For the reader's convenience, the original memorandum is reproduced below in its entirety, with the addendum clearly identified at the end of this document.

Background

Ramelteon (also known as TAK-375) is a melatonin receptor agonist with high affinity for the melatonin MT_1 and MT_2 receptors. Melatonin receptors are found in various tissues throughout the body, and are classified into three subtypes: MT_1, MT_2, and MT_3. Ramelteon, and its active metabolite, M-II, have been shown through *in vitro* assays to have little affinity for MT3, other receptors, or enzymes.

The applicant proposed that ramelteon's interaction with the melatonin receptors is the basis of the mechanism of action, since it is believed that endogenous melatonin's interaction with these receptors affects the maintenance of a normal circadian rhythm underlying the sleep-wake cycle. The applicant seeks the following indication: "[Ramelteon] is indicated for the treatment of insomnia.

The clinical review of this supplement was performed by D. Elizabeth McNeil, M.D. and the statistical review was performed by Dionne Price, Ph.D. David Lee, Ph.D., reviewed the pharmacokinetic data and Adam Wasserman, Ph.D. reviewed the pharmacology and toxicology data. Pramoda Maturu, Ph.D., performed the CMC review and Katherine Bonson, Ph.D. reviewed the abuse liability studies. A consultation response from the Division of Metabolic and Endocrine Drug Products was provided by Mary Parks, M.D. This memorandum will summarize their findings, as well as my recommendation regarding the approvability of this application.

Regulatory History

The applicant has performed numerous studies during the drug's development, including pharmacokinetic studies, drug-drug interaction studies, food-interaction studies, abuse liability studies, and studies on the effect of ramelteon on human endocrine function. Seven studies were specifically designed to evaluate ramelteon's efficacy. Safety data were collected in all the studies.

There were several interactions with the applicant prior to submission of the application, including an End-of-Phase 1 meeting, an End-of-Phase 2 meeting, a Pre-NDA meeting and several teleconferences. During these meetings, the number and types of clinical trials that would be required, as well as the study endpoints and statistical analyses that would support the indication of interest, were conveyed to the applicant.

On February 11, 2004, during a teleconference held after the End-of-Phase 2 meeting and before the Pre-NDA meeting, the applicant informed the Division that Study TL020 had failed in its primary efficacy endpoint, subjective sleep latency. They were informed that it might be possible to extrapolate efficacy to the younger population based on the results of Study TL025, which was then ongoing, but that this would depend on the results of the study. Although it is generally acknowledged that the ability to extrapolate data from one patient population to another involves multiple factors (pathophysiology, mechanism of action of the intervention, etc.), part of this process also involves an assessment of the statistical robustness and clinical significance of the findings.

At the Pre-NDA meeting the applicant informed the agency of their intention to utilize the following trials to support their proposed indication: Trials 017, 021, 023, and 025. It is appropriate for the applicant to designate which trials they consider pivotal in support of their application. It is also appropriate for the reviewing division to request and review data from *all* trials which may be contain data that will allow the assessment of safety and/or efficacy, and to make its own determination of the appropriateness of the individual studies to provide information.

The table below, adapted from Dr. McNeil's review, summarizes the studies which were reviewed to assess the efficacy and safety of ramelteon in patients.

Study, Location, and Date	*Design*	*Duration*	*Type of Patient Population*	*Primary Efficacy Endpoint*	*Treatment arms*	*No. of Patients*
			Transient insomnia			
PNFP002 14 centers in the U.S.; 5/2000 – 10/2000	Double-blind, randomized, placebo-controlled, single dose	2 days	Healthy adults (35 – 60 yrs old) with transient insomnia	Latency to persistent sleep (by PSG)	16 mg 64 mg placebo	N = 375 16 mg: 126 64 mg: 126 placebo: 123
TL023 15 centers in the U.S.; 12/02 – 5/03	Double-blind, randomized, placebo-controlled, single dose	2 days	Healthy adults (18 – 64 yrs old) naïve to a sleep laboratory environment	Latency to persistent sleep (by PSG)	8 mg 16 mg placebo	N = 289 8 mg: 98 16 mg: 94 placebo: 97
			Chronic insomnia (Objective 1° endpoint trials)			
TL005 13 centers in the U.S.; 9/01 – 2/02	Double-blind, randomized, placebo-controlled, 5-period crossover, dose response, safety and efficacy	Each period lasted 2 days, with 5 – 12 days between periods	Healthy adults (18 – 65 yrs old) with chronic insomnia	Latency to persistent sleep (by PSG)	4 mg 8 mg 16 mg 32 mg	N = 107
TL017 17 centers in the U.S.; 10/02 – 7/03	Double-blind, randomized, placebo-controlled, crossover, safety and efficacy	Each period lasted 3 days, with 5 – 12 days between periods	= 65 yrs old with chronic insomnia	Latency to persistent sleep from nights 1 and 2 of each treatment period	4 mg 8 mg placebo	N = 100
TL021 29 centers in the U.S.; 1/03 – 9/03	Double-blind, placebo-controlled, fixed dose, PSG and outpatient safety and efficacy	44 days	18-64 yrs old with chronic insomnia	Latency to persistent sleep (by PSG)	8 mg 16 mg placebo	N = 405 8 mg: 139 16 mg: 135 placebo: 131
			Chronic insomnia (Subjective 1° endpoint trials)			
TL020 79 centers in the U.S.; 1/03 – 9/03	Double-blind, randomized, placebo-controlled, fixed dose,	49 days	18 – 64 yrs old with chronic insomnia	Subjective sleep latency	8 mg 16 mg placebo	N = 848 8 mg: 277 16 mg: 284 placebo: 287

Study, Location, and Date	*Design*	*Duration*	*Type of Patient Population*	*Primary Efficacy Endpoint*	*Treatment arms*	*No. of Patients*
	safety and efficacy					
TL025 136 centers in the U.S.; 12/02 – 1/04	Double-blind, randomized, placebo-controlled, fixed dose safety and efficacy	49 days	= 65 yrs old with chronic insomnia	Subjective sleep latency	4 mg 8 mg placebo	N = 829 4 mg: 281 8 mg: 274 placebo: 274
			Long-term Safety			
TL022 123 centers in the U.S.; ongoing	Open-label, long-term safety	N/A	= 18 yrs old with chronic insomnia	N/A	8 mg: =65 yrs. old 16 mg: 19-64 yrs. old	8 mg: 248 16 mg: 965

Efficacy

Due to the number of studies involved, a detailed description of the designs of the study protocols (i.e., inclusion/exclusion criteria, assessments, efficacy parameters, and data analysis plans) will not be included in this memorandum; this can be found in Dr. McNeil's review.

Study Results – Transient insomnia

Two studies were performed to evaluate ramelteon's efficacy in a transient insomnia model, PNFP002 and TL023. Study PNFP002 utilized 16 and 64 mg of ramelteon, therefore the data derived from that study will not support the efficacy of 8 mg of ramelteon, the dose for which the applicant is seeking marketing approval. The data will be useful however, for evaluation of ramelteon's safety.

In Study TL023, analysis of the latency to persistent sleep (LPS) data for the intent-to-treat (ITT) population demonstrated statistically significant treatment effect overall when ramelteon was compared to placebo. However, when the doses were considered individually, the 8 mg treatment group maintained significance while the 16 mg treatment group did not. The table below, adapted from Dr. Price's review, summarizes the results of the change in the mean latency to persistent sleep (in minutes).

	Placebo N = 97	**Ramelteon 8 mg N = 98**	**Ramelteon 16 mg N = 93**	**Overall p-value**
LS mean (SE)	19.7 (1.87	12.2 (1.88)	14.8 (1.93)	
LS mean difference from placebo (SE)		-7.6 (2.62)	-4.9 (2.65)	0.015
95 % CI of difference		(-12.7,-2.4)	(-10.1, 0.3)	
Pairwise p-value		0.004	0.065	

It is worth noting that although the results are statistically significant, the treatment effect, as represented by the mean difference from placebo, is less than 8 minutes.

Whether this represents a treatment effect that is clinically significant is potentially up for debate.

Other observations of Study TL023 included the following:

- Gender analysis demonstrated a statistically significant difference for males at both doses, but not for females (at either dose).
- For persons < 40 years old, there was a statistically significant difference from placebo for those who were treated with the 8 mg dose, but not the 16 mg dose.
- An evaluation by ethnic group identified a statistically significant difference from placebo for Caucasians subjects treated with the 8 mg dose only.

Study Results – Chronic insomnia

Three studies evaluated the efficacy of ramelteon in chronic insomnia with LPS by polysomnography (PSG) as the primary efficacy parameter. The first two studies, Study TL005 and Study TL017, utilized a multi-period crossover design. The third, Study TL021, utilized a fixed dose design. The table below, adapted from Dr. McNeil's review, summarizes the results of the change in the mean latency to persistent sleep (in minutes).

Study Visit	Placebo	Ramelteon				Overall p-value
		4 mg	8 mg	16 mg	32 mg	
TL005	37.7	24.0*	24.3*	24.0*	22.9*	<0.001
TL017	38.4	28.7*	30.8*	--	--	<0.001
TL021						
Baseline	65.3	--	64.3	68.4	--	
Week 1	47.9	--	32.2*	28.9*	--	<0.001
Week 3	45.5	--	32.6*	27.9*	--	<0.001
Week 5	42.5	--	31.5*	29.5*	--	0.003

* - denotes statistical significance

As with the trials in transient insomnia, although the mean change in LPS compared to placebo was statistically significant, the clinical significance is questionable, for the difference for the 8 mg treatment group was never greater than ~16 minutes (Study TL021, week 1).

As noted by Dr. McNeil in her review, insomnia is different than other disorders in that both objective and subjective measurements are important, and it can be argued that from a clinical standpoint, the subjective parameters may even be more so. Studies TL005, TL017 and TL021 evaluated subjective sleep latency as one of the secondary efficacy parameters. The applicant also conducted two outpatient studies (Study TL020 and Study TL025) where the primary efficacy endpoint was subjective sleep latency. The results on this endpoint are summarized in the table below, adapted from Dr. McNeil's review.

Study Visit	Placebo	Ramelteon				Overall p-value
		4 mg	8 mg	16 mg	32 mg	
TL005	57.0	50.9	46.7	43.9*	46.5	0.040
TL017	58.2	48.2*	50.9	--	--	0.096

Study Visit	Placebo	Ramelteon				Overall p-value
		4 mg	8 mg	16 mg	32 mg	
TL021						
Baseline	74.7	--	71.4	77.8	--	--
Week 1	64.3	--	62.9	59.7	--	0.351
Week 3	61.8	--	56.6	53.4*	--	0.033
Week 5	57.1	--	52.5	53.5	--	0.325
TL020						
Baseline	85.5	--	85.2	92.5	--	--
Week 1	74.4	--	74.8	77.2	--	0.602
Week 3	70.7	--	69.5	69.3	--	0.872
Week 5	66.5	--	64.1	65.2	--	0.737
TL025						
Baseline	84.2	83.5	86.6	--	--	--
Week 1	78.5	70.2*	70.2*	--	--	0.009
Week 3	69.3	64.9	60.3*	--	--	0.013
Week 5	70.6	63.4*	57.7*	--	--	<0.001

* - denotes statistical significance

Dr. Price confirmed the applicant's analyses, and due to concerns about the imputation scheme for lost data used by the applicant, specifically a last-observation-carried-forward (LOCF) method, she re-analyzed the data using a baseline observation carried forward technique. The results of both imputation techniques were comparable.

The results for 8 mg in Study TL025 are statistically significant, but a similar observation is made regarding the clinical significance of the result, since the maximum mean difference compared to placebo is ~13 minutes.

Additional analyses performed by the applicant included a responder analysis, where a responder was defined as a participant having latency to persistent sleep less than or equal to 30 minutes. The results did not support the primary analysis at Week 1. Dr. Price reanalyze the data altering the responder definition to include only those patients who completed the study; the results were comparable to what the applicant reported.

Secondary endpoints included subjective total sleep time (sTST), sleep quality, and clinical global impression (CGI) of the change of condition. There were no significant treatment differences at any of the timepoints for sleep quality or CGI. A significant difference was seen at Weeks 1 and 3 for sTST for the 4 mg treatment group, but not the 8 mg treatment group.

Safety

The number of patients that were exposed to a particular dosage, and the duration of that exposure, is summarized in the table below. It is apparent from the table that although approximately a fifth of the patients on 8 mg had some amount of data extending to 6 months, the substantial amount of the data for the 8 mg dose are in the 7 – 35 day range.

Exposure (days)	Placebo N = 1370 (%)	< 4 mg N = 20 (%)	4 mg N = 511 (%)	8 mg N = 1250 (%)	16 mg N = 1961 (%)	32 mg N = 169 (%)	64 mg N = 209 (%)
1	306 (22.3)	20 (100)	27 (5.3)	122 (9.8)	320 (16.3)	8 (4.7)	134 (64.1)
>1 – 7	281 (20.5)	0	216 (42.3)	244 (19.5)	253 (12.9)	161 (95.3)	75 (35.9)
>7 – 35	545 (39.8)	0	220 (43)	562 (45)	516 (26.3)	0	0
>35 – 180	223 (16.3)	0	48 (9.4)	278 (22.2)	715 (36.5)	0	0
>180 days	6 (0.4)	0	0	34 (2.7)	95 (4.8)	0	0
Missing	9 (0.6)	0	0	10 (0.8)	62 (3.2)	0	0
Mean duration	24.3	1	18.5	51.2	58.5	3.3	2.9
SD	31.5	0	16.3	81	65.4	1.9	2.6

Adverse events

Deaths

There were two deaths reported in the application, both on the 16 mg treatment arm in Study TL022. The first fatality was a 57-year old woman who died on study day 159 after having been struck by a motor vehicle while walking down a highway at 2:30 in the morning; her autopsy revealed a blood ethanol level of 0.238 gm/dl. Based on her diary entries, the applicant deduced that the patient's last dose was approximately 6 weeks prior to her accident. Although it is not possible to completely rule out an association with the study drug, there is not a clear causal connection.

The second fatality was 58-year old man, who was on study day 227 when he was struck by a motor vehicle while crossing a parking lot. His last dose of medication was on the night before his accident. It was also not possible in this case to completely rule out an association with the study drug, and the case report form did not contain enough information to permit a clear causal connection.

Serious adverse events

There were 56 serious adverse events (SAEs) identified in the database, 18 of which resulted in patient discontinuation. The adverse events that resulted in discontinuation were in the 8 mg and 16 mg ramelteon treatment groups, and there was no obvious pattern to the SAEs with respect to the system organ class affected.

Most commonly reported adverse event

The most commonly reported adverse events for 8 mg of ramelteon were headache, somnolence, fatigue and dizziness, as summarized in the table below, adapted from Dr. McNeil's review.

Term	Placebo N = 1370 (%)	Ramelteon 4 mg N = 511 (%)	8 mg N = 1250 (%)	16 mg N = 1961 (%)	32 mg N = 169 (%)	64 mg N = 209 (%)
Any Adverse event	*558 (40.7)*	*191 (37.4)*	*596 (47.4)*	*928 (47.3)*	*56 (33.1)*	*74 (35.4)*
Headache NOS	92 (6.7)	22 (4.3)	88 (7)	201 (10.2)	10 (5.9)	15 (7.2)
Somnolence	45 (3.3)	13 (2.5)	58 (4.6)	204 (10.4)	4 (2.4)	17 (8.1)

Term	Placebo N = 1370 (%)	Ramelteon 4 mg N = 511 (%)	8 mg N = 1250 (%)	16 mg N = 1961 (%)	32 mg N = 169 (%)	64 mg N = 209 (%)
Fatigue	26 (1.9)	6 (1.2)	44 (3.5)	94 (4.8)	2 (1.2)	10 (4.8)
Dizziness	44 (33.2)	20 (3.9)	56 (4.5)	66 (3.4)	0	2 (1.0)
Nausea	31 (2.3)	11 (2.2)	39 (3.1)	78 (4.0)	2 (1.2)	4 (1.9)
Nasopharyngitis	35 (2.6)	8 (1.6)	34 (2.7))	95 (4.8)	1 (0.6)	1 (0.5)
Insomnia exacerbated	23 (1.7)	7 (1.4)	38 (3.0)	41 (2.1)	0	0
Upper respiratory tract infection NOS	26 (1.9)	4 (0.8)	33 (2.6)	62 (3.2)	3 (1.8)	2 (1.0)
Diarrhea NOS	24 (1.8)	5 (1.0)	24 (1.9)	37 (1.9)	1 (0.6)	3 (1.4)
Myalgia	12 (0.9)	15 (2.9)	21 (1.7)	18 (0.9)	1 (0.6)	0

Additional considerations

Pharmacology/toxicology

The non-clinical data submitted by the applicant has identified a positive finding in one *in vitro* chromosome aberration genetic toxicology study. It was negative in an *in vitro* bacterial reverse mutation (Ames) assay using *Salmonella typhinurium* and *Escherichia coli*, an *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK $^{+/-}$ cell line, an *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes, and in the *in vivo* micronucleus assays conducted in mouse and rat. Based on these results, Dr. Wasserman's conclusion is that ramelteon does not have a mutagenic or direct DNA effect, but did demonstrate clastogenecity.

The carcinogenicity assessment identified dose-dependent development of hepatic tumors in mice, including adenoma, carcinoma, and hepatoblastoma. Although the occurrence of hepatic tumors in rodent carcinogenicity studies is not uncommon, the Executive Carcinogenicity Assessment Committee (eCAC) concluded that the clinical relevance of these findings could not be excluded.

Rats treated with TAK-375 also manifested an increase in the development of hepatic tumors that was dose-dependent, but an increase in Leydig cell tumors compared to control-treated males was noted as well. The eCAC once more concluded that the clinical significance of these tumors could not be excluded.

Administration of TAK-375 to pregnant rats during organogenesis resulted in teratogenic effects: dose-dependent fetal malformations; specifically diaphragmatic hernia, cysts on the external genitalia, and irregularly shaped scapula and ribs. Although the dose of ramelteon that were required to produce the teratogenic effects were many multiples the maximum recommended human dose based on a body surface area comparison, these data require ramelteon to be designated a Pregnancy Category C.

Potential interaction in patients who are active smokers

Ramelteon was not formally assessed in patients who smoke. Since *in vitro* studies indicate that ramelteon is primarily metabolized by CYP1A2, and it is well known that

smoking will induce CYP1A2 activity, there is the possibility that smokers may have lower levels of ramelteon. What impact this could have on the efficacy of ramelteon is unknown.

Potential for drug-drug interactions
Ramelteon's metabolism is significantly hindered by CYP1A2 inhibition. An *in vivo* pharmacokinetic study assessing the interaction of fluvoxamine and ramelteon revealed that ramelteon's $AUC_{0?\ 8}$ was increased 190-fold, and the C_{max} was increased 70-fold. A study evaluating the co-administration of a CYP1A2 substrate (theophylline) demonstrated an increase in $AUC_{0?\ 8}$ of approximately 40% and in increase in C_{max} of approximately 35%.

Large inherent in vivo variability in absolute bioavailability
The absolute bioavailability of ramelteon is approximately 2%, with a range of 0.5% to 12%. This property can potentially increase the clinical implications of coadministration of ramelteon with CYP1A2 inhibitors.

Interactions with the human endocrine system
The potential effects of ramelteon on the endocrine system were evaluated in three studies: TL031 (a 4-week study), TL032 (a 6-month study), and TL022 (a long-term safety study still underway at the time of the application's submission). However, due to the short duration of Study TL031, the results observed need to be interpreted with caution, since it is unlikely that an effect on the endocrine system would be detectable in this time period. Further, although Study TL022 offered the possibility of following patients for a longer term (12 months), its lack of a control group will also limit its ability to permit any definitive conclusions to be made. As noted in Dr. Park's consultation response, any differences noted in the elderly group compared to the younger group in this study may be reflecting the underlying risks of the older age group to develop endocrine abnormalities, and not be related to drug therapy.

Study TL031
TL031 was a 4-week, randomized, double-blind, placebo-controlled, parallel-group study in healthy adult volunteers. There was a total of 99 patients randomized to either placebo or 16 mg of ramelteon (49 placebo; 50 ramelteon); 96 patients completed the study (47 placebo; 49 ramelteon). There were no significant differences reported in the mean changes from baseline in the endocrine parameters assessing thyroid function, the adrenal axis, or the reproductive axis between the treatment groups. However, as noted above, the short duration of the study limits its ability to detect any effect by ramelteon on the endocrine system.

Study TL032
TL032 was a 6-month, randomized, double-blind, placebo-controlled, parallel-group study in healthy adults with chronic insomnia. Patients were randomized to either placebo or 16 mg of ramelteon. A total of 122 patients were randomized (65 placebo; 57 ramelteon). The number of patients completing the study was low (63% in the placebo and 44% in the ramelteon group). The most common reason cited for study withdrawal

was withdrawal of informed consent and adverse events, and seemed to occur early in the course of the study.

There were no statistically significant differences noted between ramelteon and placebo for the endocrine parameters assessing thyroid function and the adrenal axis. There was a statistically significant difference in the overall mean change of prolactin levels from baseline to the end of treatment (-0.6 µg/L change in the placebo group compared to 2.9 µg/L in the ramelteon group). A higher percentage of patients on the ramelteon group had an increase in prolactin levels documented from a normal value at baseline (31.5% in the ramelteon group, 18.5% in the placebo group). Although most of these were in the range of 20 – 30 µ/L, five patients in the ramelteon group had an increase > 40 µ/L, compared to one patient in the placebo group. Based on these data alone, causality is difficult to definitively establish; however, there is published literature indicating an association between melatonin levels and prolactin elevations. Due to this possible association, continued evaluation of ramelteon's effect on prolactin levels, and its long-term consequences on bone metabolism and reproductive health should be considered.

Study TL022

TL022 is a12-month, open-label, uncontrolled, fixed-dose study. Patients were assigned to either 8 mg of ramelteon (=65 years of age), or 16 mg of ramelteon (18 – 64 years of age). For purpose of data analyses, they were categorized into one of the following:

- 24-week compliant: subjects who had taken an average of = 3 doses/week during the first 24 weeks of the study
- 48-week compliant: subjects who had taken an average of = 3 doses/week during the first 48 weeks of the study

It is important to note that due to a high dropout rate, the majority of the patients had study medication exposures of < 32 weeks; only 77 patients had a total drug exposure of 48 weeks or greater.

With respect to the findings, the incidence of abnormal thyroid function studies was comparable to what was observed in the other two studies, and may be reflective of the background rate of thyroid dysfunction. There were two patients (0.16%) with abnormal morning cortisol levels who subsequently were evaluated with ACTH stimulation testing and were found to be abnormal. There were no patients in the two controlled studies who had abnormal ACTH stimulation tests. There was a decrease in the mean Total and Free testosterone levels noted in the 8 mg dose group from baseline to Months 4 and 8, while the 16 mg group had a slight increase in mean testosterone levels over time. Without a placebo group, it is not possible to discern the significance of this finding.

The overall conclusion based on the data available to date is that the number of patients, and the duration of exposure are insufficient to exclude the possibility that ramelteon is associated with chronic hyperprolactinemia. However, due to the fact that prolactin levels can increase for a variety of reasons, routine monitoring of prolactin levels is not recommended while on ramelteon therapy, but should instead be considered as part of the

focused clinical evaluation in someone who presents with amenorrhea or sexual dysfunction.

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Pediatric patient population
The applicant had originally requested a deferral of pediatric studies during the Pre-NDA meeting. These studies should be deferred until ramelteon's impact on the endocrine system is better evaluated.

Scheduling recommendation
Based on review of the data from abuse liability studies submitted by the applicant, the Controlled Substances Staff is proposing that ramelteon not be controlled under the Controlled Substances Act. This recommendation is usually not incorporated into the decision-making process regarding the approvability of a product; however, it is important to be cognizant of the potential ramifications that, if approved, ramelteon would represent the first unscheduled hypnotic. It is highly probable that such a classification would result in different prescribing patterns, with the potential for greater patient exposures to ramelteon than other hypnotics.

Recommendations
The applicant has conducted a significant number of studies in the course of the development of ramelteon. They have been interactive with the Division at the appropriate junctures in their application. However, after approximately 3500 patients being exposed to ramelteon in various studies, the final assessment is that ramelteon has a statistically significant treatment effect that is of marginal clinical significance.

In addition to the findings that the treatment effect does not seem robust, either in the form of additional analyses, or in the case of some of the secondary efficacy endpoints, there is the observation that that ramelteon fails to demonstrate a treatment effect in the subjective efficacy parameters. The applicant proposes that ramelteon's unique mechanism of action makes it difficult for patients to appreciate the shortened LPS and increased TST provided, and the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than benzodiazepine receptor agonist. Although the applicant's proposal may be true, at this point it appears to be more speculative and not supported by any data. Furthermore, even if the applicant is correct, the end result is the same in that the patients who are currently being targeted by the proposed indication do not seem to recognize any benefit from treatment with ramelteon.

Ordinarily, a marginally clinically significant treatment effect would not preclude an approval of a product. However, the ability to approve such a product would then focus even more on the safety profile, as the risk:benefit assessment is being made.

In the case of ramelteon, there are several issues in the safety profile that are of concern. First is the observation that a significant portion of patients experienced one type of adverse event or another, highlighting that ramelteon is not an entirely benign product. Secondly, there is the observation that there appeared to be a number of patients who experienced hyperprolactinemia. Due to the number of patients exposed and the duration of exposure, it is not possible to determine whether there was a true causal relationship; however, it is also not possible to definitively exclude a relationship between the hyperprolactinemia and ramelteon therapy. Third, there is the positive result in one of the

in vitro chromosome aberration genetic toxicology studies. It is acknowledged that several other assays were negative, and it may possible that this result actually represents an erroneous finding, however, this still needs to be addressed to determine whether ramelteon is truly a genotoxic carcinogen. Lastly, the pharmacokinetic findings that indicate a large inherent *in vivo* variability and potential for drug-drug interaction portend potential difficulties in the general population.

These concerns could potentially be handled in the labeling of the product, with appropriate information, advice, and/or warning language that would help the prescriber use ramelteon most appropriately. However, that presupposes that ramelteon offers something to the patient population being proposed by the applicant. The applicant has not submitted sufficient data to support that position.

My recommendation is that the current application be deemed "Approvable." In order for this application to be approved, the applicant will be required to either identify a patient population in which the treatment effect demonstrated by ramelteon is not only statistically significant, but also of significant clinical significance to outweigh the currently known risks of ramelteon. Alternatively, the applicant can provide sufficient information to put the currently known risks of ramelteon into perspective. This would include further elucidation of the relationship of ramelteon therapy and hyperprolactinemia, and re-assessment of the positive result in the genotoxicity assay.

Depending on the additional information submitted, a decision can then be made as to whether the risk:benefit profile would support approval of ramelteon.

ADDENDUM:

The primary reviewer, D. Elizabeth McNeil, M.D., recommended an approval action based on the applicant successfully being able demonstrate that ramelteon C

J by demonstrating a decrease in the latency to persistent sleep for up to 35 days of therapy, utilizing objective measurements (i.e., polysomnography). She noted that the evidence was inconsistent when subjective measurements were used to assess ramelteon's effect on the latency to persistent sleep endpoint. Her final assessment was that ramelteon has an immediate hypnotic effect and may appropriately be used in the short-term treatment of insomnia.

As noted in my original memorandum, even though the applicant was able to demonstrate a statistically significant difference between ramelteon and placebo, it was my opinion that this statistically significant difference was not clinically meaningful. When this observation was combined with inconsistent results in the subjective measurements, which would presumably reflect what the benefit the patients felt they were obtaining from treatment with ramelteon, and the potential for an association with hyperprolactinemia, it was my opinion that the applicant had not adequately demonstrated a favorable risk:benefit ratio for the patient population in which they had expressed an interest for marketing.

My recommendation of an "approvable" action on this application is intended to reflect my opinion that ramelteon does appear to possess a certain amount efficacy, however, the applicant would need to conduct studies to identify the patient population in whom the benefit of ramelteon therapy would outweigh the currently known risks. Conversely, the applicant could perform additional studies to further elucidate ramelteons interaction with the human endocrine system, so that the ramelteon's risks could be evaluated in view of the currently known clinical benefit.

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/s/

Rigoberto Roca
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MEDICAL OFFICER
NDA 21-782

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
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DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

DATE:	July 18, 2005
DRUG:	Rozerem (ramelteon, 8-mg tablets)
NDA:	21-782
NDA Code:	Type 1S NDA
SPONSOR:	Takeda Global Research & Development Center Inc.
INDICATION:	For the treatment of insomnia

Takėda submitted NDA 21-782 in support of marketing approval for Rozerem, 8-mg tablets, on September 21, 2004.

Review of the CMC portion of this application was completed by Pramoda Maturu, Ph.D. Review of the general pharmacology and toxicology data presented in this application was completed by Adam M. Wasserman, Ph.D. Supervisory reviews were provided by Daniel Mellon, Ph.D., Supervisory Pharmacologist in this division and by Kenneth L. Hastings, Ph.D., Associate Director for Pharmacology and Toxicology, Office of Drug Evaluation II. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by Dionne Price, Ph.D. The clinical review was completed by D. Elizabeth McNeil, M.D. and a supervisory review of the clinical data was submitted by Rigoberto Roca, M.D., Deputy Director of this division. Consultation on this application was also obtained from the Division of Metabolic and Endocrine Drug Products, the Controlled Substance Staff (CSS), the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Office of Drug Safety (ODS).

Ramelteon is a melatonin receptor agonist. It has high affinity for the MT_1. and MT_2-receptor subtypes, and little affinity for the MT_3-receptor subtype or other receptors types. Its active metabolite, M-II, has a similar binding profile. Binding at the MT_1. and MT_2-receptor subtypes by melatonin is thought to affect circadian rhythms, including the sleep-wake cycle. Specifically in regard to the sleep-wake cycle, melatonin is thought to induce sleep via damping of the continuous alerting stimulus that normally arises from the suprachiasmatic nucleus. This is the basis for the original preclinical investigation of ramelteon and for the introduction of a clinical development plan. Up to and through the end of Phase 2, the IND for this product was located in the Division of Neuropharmacological Drug Products (DNDP). The IND was transferred to this division in September of 2003.

Efficacy:

Reports for seven randomized controlled clinical trials were submitted with this application. These studies have been thoroughly reviewed by Drs. McNeil, Price and Roca. Therefore, I will only briefly summarize their findings.

Transient Insomnia Studies:

Study PNFP002 (002):

This study evaluated doses of 16 and 64 mg and will not be included in the efficacy evaluation of the product.

Study TL023 (023):

This was a randomized, double-blind, placebo-controlled, parallel-group trial which compared single doses of Rozerem 8 and 16 mg to placebo in healthy adult subjects. The patients were evaluated in sleep laboratories, receiving study drug or placebo 30 minutes before their usual sleep time. The primary outcome assessment was latency to persistent sleep (LPS) as measured by polysomnography (PSG). A statistically significant treatment effect (8 minutes) was demonstrated for the 8-mg dose of Rozerem compared to placebo, but not for the 16-mg dose. A categorical analysis (proportion of subjects with LPS less than or equal to 30 minutes) performed by the sponsor did not show a treatment effect for either dose.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, number of awakenings after persistent sleep and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, restorative nature of sleep, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Only TST

and SE (measures influenced by sleep latency) showed statistically significant treatment effects. None of the subjective measures were supportive of the primary efficacy analysis.

Chronic Insomnia Studies with Objective Outcome Measures:

Study TL005 (005):

This was a randomized, double-blind, placebo-controlled, crossover, dose-response trial that compared 4, 8, 16 and 32 mg of Rozerem to placebo in otherwise healthy adult subjects with chronic insomnia. Each period lasted two days, with 5 to 12 days between periods. The primary outcome assessment was latency to persistent sleep (LPS) as measured by PSG on Nights 1 and 2 of each treatment period. A statistically significant treatment effect was demonstrated for each dose when compared to placebo. The differences in mean LPS scores ranged from 13 to 15 minutes and did not show a clear dose effect.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, and sleep quality. The objective measures were inconsistently supportive of the primary outcome assessment results. In regard to the subjective outcomes, a statistically significant result was only noted for the 16-mg group on the sleep latency measure.

Study TL017 (017):

This was a randomized, double-blind, placebo-controlled, crossover, dose-response trial that compared 4 and 8 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. Each period lasted three days, with 5 to 12 days between periods. The primary outcome assessment was latency to persistent sleep as measured by PSG on Nights 1 and 2 of each dosing period. A statistically significant treatment effect was demonstrated for each dose when compared to placebo. The difference from placebo in mean LPS scores was 10 minutes for the 4-mg group and 8 minutes for the 8-mg group.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, number of awakenings after persistent sleep and percentage of time in each sleep stage. Additional subjective measures included: time to sleep onset, total sleep time, restorative nature of sleep, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Only TST and SE (measures influenced by sleep latency) showed statistically significant treatment effects for both dose groups. There was a statistically significant increase in the number of awakenings after sleep for the 4-mg group compared to placebo. In regard to the subjective outcomes, a statistically significant result was only noted for the 4-mg group on the sleep latency measure.

Study TL021 (021):

This was a randomized, double-blind, placebo-controlled, parallel-group trial that compared 8 and 16 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. The primary outcome assessment was latency to persistent sleep as measured by PSG on two nights at Weeks 1, 3 and 5. Rebound insomnia and withdrawal were evaluated on a return visit on Nights 36 and 37. Patients were instructed to take study medication at home, nightly, between visits. There was a statistically significant treatment effect for each dose compared to placebo at each of the time periods. A categorical analysis (proportion of subjects with LPS less than or equal to 30 minutes) performed by the sponsor, and reanalyzed by Dr. Price, was mostly supportive of the primary outcome findings. No evidence of rebound insomnia or withdrawal was found.

Secondary efficacy measures included polysomnographically determined: total sleep time (TST), sleep efficiency (SE), awake time after persistent sleep, and number of awakenings after persistent sleep. Additional subjective measures included: time to sleep onset, total sleep time, awake time, number of awakenings, ease of falling back to sleep, and sleep quality. Statistically significant treatment effects for both doses were noted for SE and TST, but only at Week 1; although the 16-mg dose did show statistically significant treatment effects at Week 3. There were no statistically significant treatment effects for the 8-mg group on the subjective measures; although the 16-mg dose did show inconsistent support on these measures.

Chronic Insomnia Studies with Subjective Outcome Measures:

Study TL020 (020):

This was a randomized, double-blind, placebo-controlled, parallel-group outpatient trial that compared 8 and 16 mg of Rozerem to placebo in otherwise healthy adult subjects with chronic insomnia. The primary outcome assessment was mean subjective sleep latency over the initial seven nights of double-blind treatment. No treatment effect was demonstrated.

Study TL025 (025):

This was a randomized, double-blind, placebo-controlled, parallel-group outpatient trial that compared 4 and 8 mg of Rozerem to placebo in otherwise healthy subjects age 65 years and older with chronic insomnia. The primary outcome assessment was mean subjective sleep latency over the initial seven nights of double-blind treatment. There were statistically significant treatment effects for each dose compared to placebo (8 minutes for each dose), and the effect appeared to persist throughout Day 36 on secondary outcome analyses. A categorical analysis (proportion of subjects with LPS less than or equal to 30

minutes) performed by the sponsor did not show a treatment effect for either dose for Week 1.

No statistically significant treatment effects were found for other secondary outcome analyses such as subjective sleep quality, ease of falling back to sleep after awakening, number of awakenings, and Clinician's Clinical Global Impression. For subjective TST, a statistically significant treatment effect was only found for the 4-mg dose, and only for Weeks 1 and 3.

Clinical Safety:

A total of 3,594 subjects were exposed to Rozerem in the clinical development program. Dr. Roca's Exposure by Time table on page 7 of his review summarizes the actual data with regard to exposure, which for the doses that the sponsor proposes to recommend and market, is less than 180 for the bulk of the subjects.

Two deaths occurred in subjects exposed to Rozerem. Both subjects were killed when struck by automobiles; and the sponsor has concluded that these deaths were, therefore, unrelated to study drug. However, due to the soporific effects of Rozerem, and the not uncommon neuropsychiatric effects associated with the drug, some relation to these events cannot be completely ruled out. While one of these subjects left a diary indicating that her last dose of study drug was approximately 6 weeks prior to the accident, she was found to have a high blood ethanol level at autopsy, raising questions of substance abuse, drug-alcohol pharmacodynamic interactions, and reporter (patient) reliability.

In general, based on the adverse events noted in the clinical studies the overall safety profile of Rozerem was relatively benign. There were somewhat higher incidences of fatigue, myalgia, depression, eye pain and dyspepsia compared to placebo, but there was no dose effect for any of these adverse events. The serious adverse events and adverse events resulting in discontinuation in the Rozerem-treated subjects were similar to those that occurred in the placebo-treated subjects. There were no clinically significant differences in the adverse events reported by the younger adult and older adult subjects.

The only laboratory findings of clinical concern were related to the effects of Rozerem on the endocrinological system. Mary Parks, M.D., Deputy Director of the Division of Metabolic and Endocrine Drug Products, provided a detailed and thorough consultation on these findings. In her consult, she concludes that only the noted hyperprolactinemia was likely to be related to Rozerem exposure and to be clinically relevant. Dr. Parks notes that, while the degree of prolactin elevation was not in the range generally associated with prolactinomas, and there were no serious adverse events seen in association with the elevated levels, even mild, persistent hyperprolactinemia can result in dysregulation of the reproductive axis and consequent hypogonadism. Hypogonadism in turn may result in amenorrhea in women, and infertility and decreased libido in both sexes. Hypogonadism is also a risk factor for osteopenia and osteoporosis.

Therefore, Dr. Parks has recommended monitoring of prolactin levels in patients with clinical complaints or presentations of concern. She does not recommend routine monitoring as prolactin elevations can occur secondary to non-pathologic etiologies such as stress. Dr. Parks also recommends that, due to the fact that differences in prolactin levels were observed in only one placebo-controlled study with only 122 subjects randomized 1:1 for 6 months of treatment, monitoring in any future studies should be considered to obtain additional data on the extent and persistence of this laboratory abnormality.

In regard to the single case of prolactinoma in the Rozerem safety database, Dr. Parks notes the following in a follow-up personal communication:

> I don't think we have sufficient evidence to say that ramelteon caused or even promoted the growth of an already-present prolactinoma. Prolactinomas are the most common functional pituitary tumors...Even if we conclude that ramelteon causes hyperprolactinemia I don't think that we can then conclude that it will induce tumor growth. Recall that many medications can cause prolactin elevations by disruption of dopamine secretion or direct stimulation of prolactin receptors but will have nothing to do with inducing pituitary adenomas.

Nonclinical Safety:

In his review, Dr. Wasserman reports on the following clinically important findings from the non-clinical studies:

- Due to the relatively, and significantly lower circulating levels of M-II in the animals studied during development, and to this metabolite's high level of activity, the exposure margins for both the parent compound and M-II should be included in the package insert.
- Due to the magnitude of the increase in hepatic adenomas, carcinomas and hepatoblastomas in male mice, and adenomas and carcinomas in female mice, compared to control-treated mice and historical control data, and the finding of clastinogenicity in one genetic toxicology study, this information should be included in the package insert.
- Due to the findings of a dose-dependent increased incidence of hepatic tumors in both male and female rats compared to control-treated rats and historical controls, and the finding of an increased incidence of Leydig cell tumors compared to control-treated rats and historical controls, these data should be included in the package insert.
- Although Rozerem exposure in rats was associated with teratogenicity, there is a large margin of safety (1,892-fold) based on pharmacokinetic data; and, although the safety margin is significantly less for the M-II metabolite (45-fold), appropriate discussion in the package insert should be adequate to address these findings.

In addition, Dr. Wasserman recommends:

- Full characterization of M-II in cardiovascular safety studies should be undertaken, as in vitro studies generally did not include this active metabolite and the submitted in vivo studies either would not be expected to evaluate M-II or did not assess the level of this metabolite.
- Full characterization of the inactive metabolite M-IV should be completed, in order to satisfy requirements for a non-rodent evaluation of toxicity.
- An in vitro chromosomal aberration assay in CHL or another system should be repeated to resolve methodological problems and to confirm or refute the positive clastogenic response observed in the original study.

However, in his supervisory review, Dr. Mellon concludes the following:

- Based on the sponsor's clinical QT study at doses of 32 and 64 mg of Rozerem, no further non-clinical cardiovascular safety studies should be necessary.
- As the rat toxicology studies provided a mean plasma concentration of M-IV at the NOAEL dose that establishes a margin of safety to support the NDA, and as the concentrations of M-IV at the monkey LOAEL provided acceptable coverage, even though the plasma concentrations of M-IV that produced no adverse effects in the monkey toxicology studies were below the mean plasma levels expected in humans at the maximum recommended daily dose (not an ideal characterization), he is able to conclude that acceptable support for the safety of the metabolite has been provided.
- As the sponsor did not provide a mechanistic explanation for the positive genotoxicity findings, they must be considered valid and cannot be dismissed. However, Dr. Mellon agreed with Dr. Wasserman's conclusion that the weight of evidence suggests an overall lack of genotoxic hazard, that further studies are not required, and that the existing data may be described in the labeling.

Clinical Pharmacology and Biopharmaceutics:

In his review, Dr. Lee reports the following clinically important findings regarding Rozerem:

- Rozerem appears to have a large inherent in vivo bioavailability, with an observed standard deviation as large as 100%.
- The active metabolite, M-II, is present in human serum in concentrations 20 to 100 times higher than the parent drug; but has approximately $1/10^{th}$ and $1/5^{th}$ the affinity of Rozerem for the MT_1 and MT_2 receptor subtypes, respectively.
- Sixty-four mg of Rozerem did not prolong the QT interval in a dedicated QT study.
- Rozerem's $AUC_{0-\infty}$ and C_{max} were 97% and 86% higher, respectively, and its $T_{1/2}$ was 66% longer in older compared with younger subjects.

- M-II's $AUC_{0-\infty}$ and C_{max} were 30% and 13% higher, respectively, and its $T_{1/2}$ was 33% longer in older compared with younger subjects.
- Single- and multiple-dose exposure of 16 mg of Rozerem resulted in increases in AUCs of 3.5 to 3.6 fold and 8.0 to 10.7 fold in patients with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. (Patients with severe hepatic impairment were not studied.)
- Administration of Rozerem with food results in a 30% increase in AUC, 22% decrease in C_{max} and one-hour increase in the $T_{1/2}$.

Dr. Lee, therefore, recommends:

- Rozerem should not be taken with food.
- Elderly patients should be prescribed one-half the usual adult dose, based on the pharmacokinetic data and the fact that all of the previously approved hypnotic drug products have been approved with recommendations for reduced dosing in the elderly.
- Rozerem should be contraindicated in patients with any degree of liver impairment.

In addition, Dr. Lee recommends that:

- Rozerem should be contraindicated for use with 1A2 inhibitors, as its AUC was increased 190-fold and its C_{max} increased 70-fold in an in vitro drug-drug interaction study with fluvoxamine.
- Rozerem should be used with caution with 2C9 inhibitors, as it AUC was increased by 52% and its C_{max} was increased by 44% in an in vitro drug-drug interaction study with fluconazole; and, the AUC and C_{max} of MII were increased by 200 and 55%, respectively in that study.
- Rozerem should be contraindicated for use with 3A4 inducers, as it's AUC and C_{max} were both reduced by 80% in an in vitro drug-drug interaction study with rifampin; and, the AUC and C_{max} of MII were decreased by 89 and 81%, respectively in that study.

Finally, Dr. Lee notes that the pharmacokinetics of Rozerem have not been studied in smokers, and smoking induces CYP1A2 activity.

Chemistry, Manufacturing and Controls:

Dr. Maturu has concluded that there are no outstanding concerns regarding the chemistry, manufacturing or controls of Rozerem.

Nomenclature:

The sponsor's initial request for the trade name [ ] was evaluated by the Division of Medication Errors and Technical Support (DMETS). The DMETS review team determined that Takeda should request a new trade name due the potential for confusion with the recently approved hypnotic Lunesta. Takeda requested Rozerem as an alternative and this trade name has been found to be acceptable.

Abuse Liability, Withdrawal Phenomena and Overdose:

In her consult, Katherine Bonson, Ph.D. has concluded that Rozerem does not have abuse liability similar to that of other scheduled products indicated for the treatment of insomnia. Further, no evidence of a withdrawal phenomenon was found in the clinical studies. There were no cases of overdose in the clinical database.

Discussion:

The sponsor has provided adequate evidence of the efficacy of Rozerem as a treatment for both transient and chronic sleep onset insomnia. They have not, however, provided any evidence that their product is effective [ ] In point of fact, they did not study outcome measures that would even allow for adequate assessment [ ]. Thus the product may only be indicated for the treatment of sleep onset insomnia.

The results of the analyses of subjective improvement in sleep latency and quality of sleep were rather surprising. Only the patients in the outpatient, subjective-endpoint study in the elderly had clinically and statistically significant improvements in these measures. Below is the sponsor's hypothesis for why there was an absence of subjective improvement in the younger adults:

> In contrast to objective measurements by PSG, subjective assessments of sleep may be influenced by other factors. Subjects with insomnia tend to overestimate sleep latency and underestimate sleep duration relative to PSG measurement...PSG changes can be measured even before the subject perceives sleepiness .... Subjects who are experienced with the use of benzodiazepines, in particular, may anticipate cues such as sedation and equate these sensations with falling asleep...Subjects treated with BZRAs may also underestimate sleep latency due to amnesic effects, forgetting how long they remained awake before falling asleep. This is analogous to preoperative use of benzodiazepines, which may produce anterograde amnesia...Given that the subjective assessment techniques in these studies were originally developed for compounds with GABAergic mechanisms of action, the absence of subjective anxiolytic, sedative, and muscle-relaxant effects prior to sleep onset may make the sleep-promoting effects of ramelteon more difficult to detect subjectively.
>
> [Application Summary: Section 2.5; Part 4.0; Overview of Efficacy]

While this is a most interesting hypothesis and may well be the explanation for the unusual results, it is only a hypothesis. Nevertheless, I think that, as there is some evidence of subjective improvement in the older adults, and considering the relatively benign safety profile of Rozerem, it is reasonable to allow marketing of the product. Patients who are dissatisfied with the efficacy of the product will simply discontinue taking the medication.

The product's potential for causing hyperprolactinemia, and resultant hypogonadism, amenorrhea, infertility, decreased libido, osteopenia and osteoporosis, is of some concern. However, as Dr. Parks has concluded, patients presenting with symptoms or signs suggestive of this abnormality can be tested, and the drug discontinued. Therefore, it is unlikely that there will be significant residual morbidity. I do not think that post-marketing studies to evaluate the persistence and extent of hyperprolactinemia and the incidence of neoplasia, as recommended by Dr. McNeil, are necessary. However, I do recognize and agree with her concern regarding this effect, and, as such, it will be important to closely watch for any signals of more significant morbidity in the post-marketing period. Both the sponsor and the Division (working closely with the Office of Drug Safety), should regularly monitor the post-marketing reports for any of these abnormalities in the initial five years after approval, and continue observation over the long term to rule out any significant increases in osteoporosis in patients treated chronically with Rozerem. It should be noted that chronic treatment will be an off-label use of this product.

I do not agree with Dr. Roca's assessment that the sponsor has not provided evidence of clinical significance in their studies. While the mean differences in latency to sleep onset were small, this is not unusual for analyses that compare the means of different treatment groups. Indeed, review of the raw data demonstrates a wide range of outcomes, many of indisputable clinical relevance.

I agree with Dr. Mellon's conclusions and recommendations that further studies, as recommended by Drs. Wasserman and McNeil, are not necessary to assess the genotoxicity, carcinogenicity or reproductive toxicity of Rozerem. Nor do I think that the pregnancy registry recommended by Dr. McNeil is warranted, based on the large margin of safety found for the teratogenic effects of the drug.

I agree with Dr. Lee's recommendation that Rozerem should be contraindicated for use with CYP1A2 inhibitors due to the extremely large increases in the C_{max} and AUC of Rozerem when it was studied with fluvoxamine. I also agree that caution is warranted when it is administered with CYP2C9 inhibitors, and that practitioners should be alerted to the fact that there could be a decrease in or loss of efficacy when it is administered with CYP3A4 inducers; although I do not agree that is necessary to contraindicate co-administration of CYP3A4 inducers, as lack of efficacy should simply result in discontinuation of treatment. Nor do I agree with Dr. Lee that is necessary to contraindicate the use of Rozerem in all patients with hepatic disease. The increases in AUC in mild hepatic impairment are small and should not result in serum concentrations

outside of the range associated with the doses studied in the clinical trials; and at those doses there were no major safety concerns and there was no evidence of excessive somnolence on the mornings after treatment.

I do not think that it is necessary to reduce the dose for elderly patients, as recommended by Dr. Lee. There were no clinically relevant differences in the safety profiles of the younger and older adult subjects in the clinical safety database. The fact that the previously approved hypnotic products have all had dosing recommendations that included a reduced dose for elderly patients is irrelevant, as Rozerem has a completely different (and novel) mechanism of action from the gabaergic hypnotics. The higher serum concentrations in the elderly subjects that were noted in the pharmacokinetic evaluations, however, should be noted in the package insert.

Based on the data provided by the sponsor in this application, I have concluded that there is a reasonable risk to benefit ratio for Rozerem, if it is used in accordance with the product labeling.

Action recommended by the Division:

Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER

CLINICAL REVIEW ADDENDUM

Application Type	NDA 21-782
Submission Number	000
Submission Code	N
Letter Date	September 21 2004
Stamp Date	September 21 2004
PDUFA Goal Date	July 23 2005
Reviewer Name	D. Elizabeth McNeil, MD
Addendum Date	July 22 2005
Established Name	Ramelteon
(Proposed) Trade Name	
Therapeutic Class	Hypnotic
Applicant	Takeda
Priority Designation	S
Formulation	Tablet
Dosing Regimen	One tablet nightly
Indication	Insomnia

The following tables provide supplementary information on adverse events seen during the development program for Ramelteon. The information in these tables comes from the placebo-controlled chronic insomnia studies (005, 017, 020, 021, 025):

I. SAEs compared to placebo in the controlled trials

Table 2.k Serious Adverse Events: Chronic Insomnia Studies

MedDRA Preferred Term	Placebo (n=897)	Ramelteon 4 mg (n=486)	Ramelteon 8 mg (n=896) 16 mg (n=528)	Ramelteon 32 mg (n=105)	All Doses of Ramelteon (n=1599)
Any serious adverse event n (%)	3 (0.3%)	2 (0.4%)	3 (0.3%) 2 (0.4%)	0	7 (0.4%)
Atrial fibrillation	0	0	1 (0.1%) 0	0	1 (0.1%)
Atrial fibrillation aggravated	1 (0.1%)	0	0 0	0	0
Myocardial ischemia	0	1 (0.2%)	0 0	0	1 (0.1%)
Gastrointestinal hemorrhage NOS	0	0	0 1 (0.2%)	0	1 (0.1%)
Cellulitis	0	0	1 (0.1%) 0	0	1 (0.1%)
Jaw fracture	1 (0.1%)	0	0 0	0	0
Dehydration	0	0	1 (0.1%) 0	0	1 (0.1%)
Hyponatremia	0	0	1 (0.1%) 0	0	1 (0.1%)
Arthritis NOS	0	0	1 (0.1%) 0	0	1 (0.1%)
Lung cancer (stage unspecified)	1 (0.1%)	0	0 0	0	0
Amnesia	0	1 (0.2%)	0 0	0	1 (0.1%)
Convulsions NOS	0	0	0 1 (0.2%)	0	1 (0.1%)
Syncope	1 (0.1%)	0	0 0	0	0
Transient ischemic attack	0	0	1 (0.1%) 0	0	1 (0.1%)

Modification of IAS Table 22.4.8.2.

II. Discontinuations for AEs compared to placebo in the chronic insomnia trials

Table 5.b Disposition of Subjects in Chronic Insomnia Studies

Placebo (n=750)		Ramelteon 4 mg (n=334)	Ramelteon 8 mg (n=741)	Ramelteon 16 mg (n=444)	Ramelteon 32 mg (n=22)	All Doses of Ramelteon (n=1541)
Completed double-blind period	642 (85.6%)	284 (85.0%)	639 (86.2%)	386 (86.9%)	22 (100.0%)	1331 (86.4%)
Discontinued	108 (14.4%)	50 (15.0%)	102 (13.8%)	58 (13.1%)	0	210 (13.6%)
Adverse event	17 (2.3%)	9 (2.7%)	18 (2.4%)	13 (2.9%)	0	40 (2.6%)
Lack of efficacy	28 (3.7%)	14 (4.2%)	19 (2.6%)	5 (1.1%)	0	38 (2.5%)
Protocol deviation	18 (2.4%)	16 (4.8%)	29 (3.9%)	10 (2.3%)	0	55 (3.6%)
Withdrawal of consent	28 (3.7%)	7 (2.1%)	24 (3.2%)	14 (3.2%)	0	45 (2.9%)
Lost to follow-up	6 (0.8%)	1 (0.3%)	6 (0.8%)	11 (2.5%)	0	18 (1.2%)
Investigator discretion	1 (0.1%)	1 (0.3%)	0	0	0	1 (0.1%)
Study termination	1 (0.1%)	0	0	0	0	0
Other	9 (1.2%)	2 (0.6%)	6 (0.8%)	5 (1.1%)	0	13 (0.8%)

Source: Table 22.2.1.2.

III. Overall AE compared to placebo in the chronic insomnia trials

Table 6.1 Adverse Events Reported for 1% or More Subjects Who Received Ramelteon: Chronic Insomnia Studies

MedDRA Preferred Term	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)
Any adverse event	391 (43.6%)	187 (38.5%)	412 (46.0%)	249 (47.2%)	21 (20.0%)	824 (51.5%)
Headache NOS	65 (7.2%)	22 (4.5%)	81 (9.0%)	57 (10.8%)	6 (5.7%)	159 (9.9%)
Somnolence	22 (2.5%)	12 (2.5%)	38 (4.2%)	37 (7.0%)	2 (1.9%)	88 (5.5%)
Dizziness	35 (3.9%)	20 (4.1%)	42 (4.7%)	11 (2.1%)	0	73 (4.6%)
Insomnia exacerbated	23 (2.6%)	7 (1.4%)	33 (3.7%)	24 (4.5%)	0	64 (4.0%)
Fatigue	22 (2.5%)	5 (1.0%)	36 (4.0%)	16 (3.0%)	2 (1.9%)	58 (3.6%)
Nausea	25 (2.8%)	11 (2.3%)	25 (2.8%)	20 (3.8%)	1 (1.0%)	54 (3.4%)
Myalgia	10 (1.1%)	15 (3.1%)	18 (2.0%)	10 (1.9%)	1 (1.0%)	44 (2.8%)
Nasopharyngitis	22 (2.5%)	8 (1.6%)	18 (2.0%)	13 (2.5%)	1 (1.0%)	40 (2.5%)
Depression	8 (0.9%)	10 (2.1%)	19 (2.1%)	6 (1.1%)	0	35 (2.2%)
Dysgeusia	18 (2.0%)	8 (1.6%)	23 (2.6%)	3 (0.6%)	0	34 (2.1%)
Eye pain	9 (1.0%)	11 (2.3%)	12 (1.3%)	7 (1.3%)	0	30 (1.9%)
Diarrhea NOS	20 (2.2%)	5 (1.0%)	16 (1.8%)	9 (1.7%)	0	29 (1.8%)
Upper respiratory tract infection NOS	19 (2.1%)	4 (0.8%)	20 (2.2%)	5 (0.9%)	0	29 (1.8%)
Pharyngitis	11 (1.2%)	4 (0.8%)	13 (1.5%)	7 (1.3%)	4 (3.8%)	27 (1.7%)
Dyspepsia	5 (0.6%)	4 (0.8%)	10 (1.1%)	8 (1.5%)	2 (1.9%)	24 (1.5%)
Dry mouth	16 (1.8%)	7 (1.4%)	12 (1.3%)	3 (0.6%)	0	22 (1.4%)
Photophobia	8 (0.9%)	6 (1.2%)	12 (1.3%)	4 (0.8%)	0	22 (1.4%)
Back pain	10 (1.1%)	4 (0.8%)	11 (1.2%)	6 (1.1%)	0	21 (1.3%)
Muscle twitching	4 (0.4%)	8 (1.6%)	11 (1.2%)	1 (0.2%)	0	20 (1.3%)
Pruritus NOS	8 (0.9%)	8 (1.6%)	8 (0.9%)	3 (0.6%)	0	19 (1.2%)
Appetite decreased NOS	2 (0.2%)	7 (1.4%)	8 (0.9%)	3 (0.6%)	0	18 (1.1%)
Arthralgia	9 (1.0%)	4 (0.8%)	10 (1.1%)	4 (0.8%)	0	18 (1.1%)
Paresthesia	10 (1.1%)	6 (1.2%)	9 (1.0%)	3 (0.6%)	0	18 (1.1%)
Sinusitis NOS	3 (0.3%)	6 (1.2%)	4 (0.4%)	7 (1.3%)	0	17 (1.1%)
Nasal congestion	6 (0.7%)	5 (1.0%)	4 (0.4%)	6 (1.1%)	1 (1.0%)	16 (1.0%)

Source: Table 22.4.3.2.1.

The information in the tables above does not change any of the conclusions regarding the adverse event profile for ramelteon as described in my review or in the label.

Additions to the label:
I have made modifications to the label in the precautions section as well as the pediatric use section to address the concern that due to the apparent effect on reproductive hormones in adults, further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent humans.

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

/s/

Dawn McNeil
7/22/05 03:35:10 PM
MEDICAL OFFICER

The information in this addendum was discussed with Drs. Roca and Rappaport, and provided to them via email on July 11th.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

Medical Officer Team Leader Memorandum

Date: June 30, 2005

To: File, NDA 21-782

From: Rigoberto Roca, M.D.
Deputy Director
Division of Anesthetic, Critical Care and Addiction Drug Products

Re: NDA 21-782: Ramelteon (TAK-375)
Takeda Global Research and Development, Inc.

Background

Ramelteon (also known as TAK-375) is a melatonin receptor agonist with high affinity for the melatonin MT_1 and MT_2 receptors. Melatonin receptors are found in various tissues throughout the body, and are classified into three subtypes: MT_1, MT_2, and MT_3. Ramelteon, and its active metabolite, M-II, have been shown through *in vitro* assays to have little affinity for MT3, other receptors, or enzymes.

The applicant proposed that ramelteon's interaction with the melatonin receptors is the basis of the mechanism of action, since it is believed that endogenous melatonin's interaction with these receptors affects the maintenance of a normal circadian rhythm underlying the sleep-wake cycle. The applicant seeks the following indication: "[Ramelteon] is indicated for the treatment of insomnia. [Ramelteon] has been shown to decrease the time to sleep onset [redacted] in controlled clinical trials."

The clinical review of this supplement was performed by D. Elizabeth McNeil, M.D. and the statistical review was performed by Dionne Price, Ph.D. David Lee, Ph.D., reviewed the pharmacokinetic data and Adam Wasserman, Ph.D. reviewed the pharmacology and toxicology data. Pramoda Maturu, Ph.D., performed the CMC review and Katherine Bonson, Ph.D. reviewed the abuse liability studies. A consultation response from the Division of Metabolic and Endocrine Drug Products was provided by Mary Parks, M.D. This memorandum will summarize their findings, as well as my recommendation regarding the approvability of this application.

Regulatory History

The applicant has performed numerous studies during the drug's development, including pharmacokinetic studies, drug-drug interaction studies, food-interaction studies, abuse liability studies, and studies on the effect of ramelteon on human endocrine function. Seven studies were specifically designed to evaluate ramelteon's efficacy. Safety data were collected in all the studies.

There were several interactions with the applicant prior to submission of the application, including an End-of-Phase 1 meeting, an End-of-Phase 2 meeting, a Pre-NDA meeting and several teleconferences. During these meetings, the number and types of clinical trials that would be required, as well as the study endpoints and statistical analyses that would support the indication of interest, were conveyed to the applicant.

On February 11, 2004, during a teleconference held after the End-of-Phase 2 meeting and before the Pre-NDA meeting, the applicant informed the Division that Study TL020 had failed in its primary efficacy endpoint, subjective sleep latency. They were informed that it might be possible to extrapolate efficacy to the younger population based on the results of Study TL025, which was then ongoing, but that this would depend on the results of the study. Although it is generally acknowledged that the ability to extrapolate data from one patient population to another involves multiple factors (pathophysiology, mechanism of action of the intervention, etc.), part of this process also involves an assessment of the statistical robustness and clinical significance of the findings.

At the Pre-NDA meeting the applicant informed the agency of their intention to utilize the following trials to support their proposed indication: Trials 017, 021, 023, and 025. It is appropriate for the applicant to designate which trials they consider pivotal in support of their application. It is also appropriate for the reviewing division to request and review data from *all* trials which may be contain data that will allow the assessment of safety and/or efficacy, and to make its own determination of the appropriateness of the individual studies to provide information.

The table below, adapted from Dr. McNeil's review, summarizes the studies which were reviewed to assess the efficacy and safety of ramelteon in patients.

Study, Location, and Date	*Design*	*Duration*	*Type of Patient Population*	*Primary Efficacy Endpoint*	*Treatment arms*	*No. of Patients*
			Transient Insomnia			
PNFP002 14 centers in the U.S.; 5/2000 – 10/2000	Double-blind, randomized, placebo-controlled, single dose	2 days	Healthy adults (35 – 60 yrs old) with transient insomnia	Latency to persistent sleep (by PSG)	16 mg 64 mg placebo	N = 375 16 mg: 126 64 mg: 126 placebo: 123
TL023 15 centers in the U.S.; 12/02 - 5/03	Double-blind, randomized, placebo-controlled,	2 days	Healthy adults (18 – 64 yrs old) naïve to a sleep laboratory	Latency to persistent sleep (by PSG)	8 mg 16 mg placebo	N = 289 8 mg: 98 16 mg: 94 placebo: 97

Study, Location, and Date	*Design*	*Duration*	*Type of Patient Population*	*Primary Efficacy Endpoint*	*Treatment arms*	*No. of Patients*
	single dose		environment			
Chronic insomnia (Objective 1° endpoint trials)						
TL005 13 centers in the U.S.; 9/01 – 2/02	Double-blind, randomized, placebo-controlled, 5-period crossover, dose response, safety and efficacy	Each period lasted 2 days, with 5 – 12 days between periods	Healthy adults (18 – 65 yrs old) with chronic insomnia	Latency to persistent sleep (by PSG)	4 mg 8 mg 16 mg 32 mg	N = 107
TL017 17 centers in the U.S.; 10/02 – 7/03	Double-blind, randomized, placebo-controlled, crossover, safety and efficacy	Each period lasted 3 days, with 5 – 12 days between periods	= 65 yrs old with chronic insomnia	Latency to persistent sleep from nights 1 and 2 of each treatment period	4 mg 8 mg placebo	N = 100
TL021 29 centers in the U.S.; 1/03 – 9/03	Double-blind, placebo-controlled, fixed dose, PSG and outpatient safety and efficacy	44 days	18-64 yrs old with chronic insomnia	Latency to persistent sleep (by PSG)	8 mg 16 mg placebo	N = 405 8 mg: 139 16 mg: 135 placebo: 131
Chronic insomnia (Subjective 1° endpoint trials)						
TL020 79 centers in the U.S.; 1/03 – 9/03	Double-blind, randomized, placebo-controlled, fixed dose, safety and efficacy	49 days	18 – 64 yrs old with chronic insomnia	Subjective sleep latency	8 mg 16 mg placebo	N = 848 8 mg: 277 16 mg: 284 placebo: 287
TL025 136 centers in the U.S.; 12/02 1/04	Double-blind, randomized, placebo-controlled, fixed dose safety and efficacy	49 days	= 65 yrs old with chronic insomnia	Subjective sleep latency	4 mg 8 mg placebo	N = 829 4 mg: 281 8 mg: 274 placebo: 274
Long-term Safety						
TL022 123 centers in the U.S.; ongoing	Open-label, long-term safety	N/A	= 18 yrs old with chronic insomnia	N/A	8 mg: =65 yrs. old 16 mg: 19-64 yrs. old	8 mg: 248 16 mg: 965

Efficacy

Due to the number of studies involved, a detailed description of the designs of the study protocols (i.e., inclusion/exclusion criteria, assessments, efficacy parameters, and data analysis plans) will not be included in this memorandum; this can be found in Dr. McNeil's review.

Study Results – Transient insomnia

Two studies were performed to evaluate ramelteon's efficacy in a transient insomnia model, PNFP002 and TL023. Study PNFP002 utilized 16 and 64 mg of ramelteon, therefore the data derived from that study will not support the efficacy of 8 mg of ramelteon, the dose for which the applicant is seeking marketing approval. The data will be useful however, for evaluation of ramelteon's safety.

In Study TL023, analysis of the latency to persistent sleep (LPS) data for the intent-to-treat (ITT) population demonstrated statistically significant treatment effect overall when ramelteon was compared to placebo. However, when the doses were considered individually, the 8 mg treatment group maintained significance while the 16 mg treatment group did not. The table below, adapted from Dr. Price's review, summarizes the results of the change in the mean latency to persistent sleep (in minutes).

	Placebo N = 97	**Ramelteon 8 mg N = 98**	**Ramelteon 16 mg N = 93**	**Overall p-value**
LS mean (SE)	19.7 (1.87	12.2 (1.88)	14.8 (1.93)	
LS mean difference from placebo (SE)		-7.6 (2.62)	-4.9 (2.65)	0.015
95 % CI of difference		(-12.7,-2.4)	(-10.1, 0.3)	
Pairwise p-value		0.004	0.065	

It is worth noting that although the results are statistically significant, the treatment effect, as represented by the mean difference from placebo, is less than 8 minutes. Whether this represents a treatment effect that is clinically significant is potentially up for debate.

Other observations of Study TL023 included the following:

- Gender analysis demonstrated a statistically significant difference for males at both doses, but not for females (at either dose).
- For persons < 40 years old, there was a statistically significant difference from placebo for those who were treated with the 8 mg dose, but not the 16 mg dose.
- An evaluation by ethnic group identified a statistically significant difference from placebo for Caucasians subjects treated with the 8 mg dose only.

Study Results – Chronic insomnia

Three studies evaluated the efficacy of ramelteon in chronic insomnia with LPS by polysomnography (PSG) as the primary efficacy parameter. The first two studies, Study TL005 and Study TL017, utilized a multi-period crossover design. The third, Study

TL021, utilized a fixed dose design. The table below, adapted from Dr. McNeil's review, summarizes the results of the change in the mean latency to persistent sleep (in minutes).

Study Visit	Placebo	Ramelteon				Overall p-value
		4 mg	8 mg	16 mg	32 mg	
TL005	37.7	24.0*	24.3*	24.0*	22.9*	<0.001
TL017	38.4	28.7*	30.8*	--	--	<0.001
TL021						
Baseline	65.3	--	64.3	68.4	--	
Week 1	47.9	--	32.2*	28.9*	--	<0.001
Week 3	45.5	--	32.6*	27.9*	--	<0.001
Week 5	42.5	--	31.5*	29.5*	--	0.003

* - denotes statistical significance

As with the trials in transient insomnia, although the mean change in LPS compared to placebo was statistically significant, the clinical significance is questionable, for the difference for the 8 mg treatment group was never greater than ~16 minutes (Study TL021, week 1).

As noted by Dr. McNeil in her review, insomnia is different than other disorders in that both objective and subjective measurements are important, and it can be argued that from a clinical standpoint, the subjective parameters may even be more so. Studies TL005, TL017 and TL021 evaluated subjective sleep latency as one of the secondary efficacy parameters. The applicant also conducted two outpatient studies (Study TL020 and Study TL025) where the primary efficacy endpoint was subjective sleep latency. The results on this endpoint are summarized in the table below, adapted from Dr. McNeil's review.

Study Visit	Placebo	Ramelteon				Overall p-value
		4 mg	8 mg	16 mg	32 mg	
TL005	57.0	50.9	46.7	43.9*	46.5	0.040
TL017	58.2	48.2*	50.9	--	--	0.096
TL021						
Baseline	74.7	--	71.4	77.8	--	--
Week 1	64.3	--	62.9	59.7	--	0.351
Week 3	61.8	--	56.6	53.4*	--	0.033
Week 5	57.1	--	52.5	53.5	--	0.325
TL020						
Baseline	85.5	--	85.2	92.5	--	--
Week 1	74.4	--	74.8	77.2	--	0.602
Week 3	70.7	--	69.5	69.3	--	0.872
Week 5	66.5	--	64.1	65.2	--	0.737
TL025						
Baseline	84.2	83.5	86.6	--	--	--
Week 1	78.5	70.2*	70.2*	--	--	0.009
Week 3	69.3	64.9	60.3*	--	--	0.013
Week 5	70.6	63.4*	57.7*	--	--	<0.001

* - denotes statistical significance

Dr. Price confirmed the applicant's analyses, and due to concerns about the imputation scheme for lost data used by the applicant, specifically a last-observation-carried-forward (LOCF) method, she re-analyzed the data using a baseline observation carried forward technique. The results of both imputation techniques were comparable.

The results for 8 mg in Study TL025 are statistically significant, but a similar observation is made regarding the clinical significance of the result, since the maximum mean difference compared to placebo is ~13 minutes.

Additional analyses performed by the applicant included a responder analysis, where a responder was defined as a participant having latency to persistent sleep less than or equal to 30 minutes. The results did not support the primary analysis at Week 1. Dr. Price reanalyze the data altering the responder definition to include only those patients who completed the study; the results were comparable to what the applicant reported.

Secondary endpoints included subjective total sleep time (sTST), sleep quality, and clinical global impression (CGI) of the change of condition. There were no significant treatment differences at any of the timepoints for sleep quality or CGI. A significant difference was seen at Weeks 1 and 3 for sTST for the 4 mg treatment group, but not the 8 mg treatment group.

Safety

The number of patients that were exposed to a particular dosage, and the duration of that exposure, is summarized in the table below. It is apparent from the table that although approximately a fifth of the patients on 8 mg had some amount of data extending to 6 months, the substantial amount of the data for the 8 mg dose are in the 7 – 35 day range.

Exposure (days)	Placebo N = 1370 (%)	< 4 mg N = 20 (%)	4 mg N = 511 (%)	8 mg N = 1250 (%)	16 mg N = 1961 (%)	32 mg N = 169 (%)	64 mg N = 209 (%)
1	306 (22.3)	20 (100)	27 (5.3)	122 (9.8)	320 (16.3)	8 (4.7)	134 (64.1)
>1 – 7	281 (20.5)	0	216 (42.3)	244 (19.5)	253 (12.9)	161 (95.3)	75 (35.9)
>7 – 35	545 (39.8)	0	220 (43)	562 (45)	516 (26.3)	0	0
>35 – 180	223 (16.3)	0	48 (9.4)	278 (22.2)	715 (36.5)	0	0
>180 days	6 (0.4)	0	0	34 (2.7)	95 (4.8)	0	0
Missing	9 (0.6)	0	0	10 (0.8)	62 (3.2)	0	0
Mean duration	24.3	1	18.5	51.2	58.5	3.3	2.9
SD	31.5	0	16.3	81	65.4	1.9	2.6

Adverse events

Deaths

There were two deaths reported in the application, both on the 16 mg treatment arm in Study TL022. The first fatality was a 57-year old woman who died on study day 159 after having been struck by a motor vehicle while walking down a highway at 2:30 in the morning; her autopsy revealed a blood ethanol level of 0.238 gm/dl. Based on her diary entries, the applicant deduced that the patient's last dose was approximately 6 weeks prior to her accident. Although it is not possible to completely rule out an association with the study drug, there is not a clear causal connection.

The second fatality was 58-year old man, who was on study day 227 when he was struck by a motor vehicle while crossing a parking lot. His last dose of medication was on the night before his accident. It was also not possible in this case to completely rule out an association with the study drug, and the case report form did not contain enough information to permit a clear causal connection.

Serious adverse events

There were 56 serious adverse events (SAEs) identified in the database, 18 of which resulted in patient discontinuation. The adverse events that resulted in discontinuation were in the 8 mg and 16 mg ramelteon treatment groups, and there was no obvious pattern to the SAEs with respect to the system organ class affected.

Most commonly reported adverse event

The most commonly reported adverse events for 8 mg of ramelteon were headache, somnolence, fatigue and dizziness, as summarized in the table below, adapted from Dr. McNeil's review.

Term	Placebo N = 1370 (%)	Ramelteon 4 mg N = 511 (%)	8 mg N = 1250 (%)	16 mg N = 1961 (%)	32 mg N = 169 (%)	64 mg N = 209 (%)
Any Adverse event	*558 (40.7)*	*191 (37.4)*	*596 (47.4)*	*928 (47.3)*	*56 (33.1)*	*74 (35.4)*
Headache NOS	92 (6.7)	22 (4.3)	88 (7)	201 (10.2)	10 (5.9)	15 (7.2)
Somnolence	45 (3.3)	13 (2.5)	58 (4.6)	204 (10.4)	4 (2.4)	17 (8.1)
Fatigue	26 (1.9)	6 (1.2)	44 (3.5)	94 (4.8)	2 (1.2)	10 (4.8)
Dizziness	44 (33.2)	20 (3.9)	56 (4.5)	66 (3.4)	0	2 (1.0)
Nausea	31 (2.3)	11 (2.2)	39 (3.1)	78 (4.0)	2 (1.2)	4 (1.9)
Nasopharyngitis	35 (2.6)	8 (1.6)	34 (2.7))	95 (4.8)	1 (0.6)	1 (0.5)
Insomnia exacerbated	23 (1.7)	7 (1.4)	38 (3.0)	41 (2.1)	0	0
Upper respiratory tract infection NOS	26 (1.9)	4 (0.8)	33 (2.6)	62 (3.2)	3 (1.8)	2 (1.0)
Diarrhea NOS	24 (1.8)	5 (1.0)	24 (1.9)	37 (1.9)	1 (0.6)	3 (1.4)
Myalgia	12 (0.9)	15 (2.9)	21 (1.7)	18 (0.9)	1 (0.6)	0

Additional considerations

Pharmacology/toxicology

The non-clinical data submitted by the applicant has identified a positive finding in one *in vitro* chromosome aberration genetic toxicology study. It was negative in an *in vitro* bacterial reverse mutation (Ames) assay using *Salmonella typhinurium* and *Escherichia coli*, an *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK $^{+/-}$ cell line, an *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes, and in the *in vivo* micronucleus assays conducted in mouse and rat. Based on these results, Dr. Wasserman's conclusion is that ramelteon does not have a mutagenic or direct DNA effect, but did demonstrate clastogenecity.

The carcinogenicity assessment identified dose-dependent development of hepatic tumors in mice, including adenoma, carcinoma, and hepatoblastoma. Although the occurrence of hepatic tumors in rodent carcinogenicity studies is not uncommon, the Executive Carcinogenicity Assessment Committee (eCAC) concluded that the clinical relevance of these findings could not be excluded.

Rats treated with TAK-375 also manifested an increase in the development of hepatic tumors that was dose-dependent, but an increase in Leydig cell tumors compared to control-treated males was noted as well. The eCAC once more concluded that the clinical significance of these tumors could not be excluded.

Administration of TAK-375 to pregnant rats during organogenesis resulted in teratogenic effects: dose-dependent fetal malformations; specifically diaphragmatic hernia, cysts on the external genitalia, and irregularly shaped scapula and ribs. Although the dose of ramelteon that were required to produce the teratogenic effects were many multiples the maximum recommended human dose based on a body surface area comparison, these data require ramelteon to be designated a Pregnancy Category C.

Potential interaction in patients who are active smokers
Ramelteon was not formally assessed in patients who smoke. Since *in vitro* studies indicate that ramelteon is primarily metabolized by CYP1A2, and it is well known that smoking will induce CYP1A2 activity, there is the possibility that smokers may have lower levels of ramelteon. What impact this could have on the efficacy of ramelteon is unknown.

Potential for drug-drug interactions
Ramelteon's metabolism is significantly hindered by CYP1A2 inhibition. An *in vivo* pharmacokinetic study assessing the interaction of fluvoxamine and ramelteon revealed that ramelteon's $AUC_{0?\ 8}$ was increased 190-fold, and the C_{max} was increased 70-fold. A study evaluating the co-administration of a CYP1A2 substrate (theophylline) demonstrated an increase in $AUC_{0?\ 8}$ of approximately 40% and in increase in C_{max} of approximately 35%.

Large inherent in vivo variability in absolute bioavailability
The absolute bioavailability of ramelteon is approximately 2%, with a range of 0.5% to 12%. This property can potentially increase the clinical implications of coadministration of ramelteon with CYP1A2 inhibitors.

Interactions with the human endocrine system
The potential effects of ramelteon on the endocrine system were evaluated in three studies: TL031 (a 4-week study), TL032 (a 6-month study), and TL022 (a long-term safety study still underway at the time of the application's submission). However, due to the short duration of Study TL031, the results observed need to be interpreted with caution, since it is unlikely that an effect on the endocrine system would be detectable in this time period. Further, although Study TL022 offered the possibility of following patients for a longer term (12 months), its lack of a control group will also limit its ability to permit any definitive conclusions to be made. As noted in Dr. Park's consultation response, any differences noted in the elderly group compared to the younger group in this study may be reflecting the underlying risks of the older age group to develop endocrine abnormalities, and not be related to drug therapy.

Study TL031
TL031 was a 4-week, randomized, double-blind, placebo-controlled, parallel-group study in healthy adult volunteers. There was a total of 99 patients randomized to either placebo or 16 mg of ramelteon (49 placebo; 50 ramelteon); 96 patients completed the study (47 placebo; 49 ramelteon). There were no significant differences reported in the mean changes from baseline in the endocrine parameters assessing thyroid function, the adrenal axis, or the reproductive axis between the treatment groups. However, as noted above, the short duration of the study limits its ability to detect any effect by ramelteon on the endocrine system.

Study TL032

TL032 was a 6-month, randomized, double-blind, placebo-controlled, parallel-group study in healthy adults with chronic insomnia. Patients were randomized to either placebo or 16 mg of ramelteon. A total of 122 patients were randomized (65 placebo; 57 ramelteon). The number of patients completing the study was low (63% in the placebo and 44% in the ramelteon group). The most common reason cited for study withdrawal was withdrawal of informed consent and adverse events, and seemed to occur early in the course of the study.

There were no statistically significant differences noted between ramelteon and placebo for the endocrine parameters assessing thyroid function and the adrenal axis. There was a statistically significant difference in the overall mean change of prolactin levels from baseline to the end of treatment (-0.6 µg/L change in the placebo group compared to 2.9 µg/L in the ramelteon group). A higher percentage of patients on the ramelteon group had an increase in prolactin levels documented from a normal value at baseline (31.5% in the ramelteon group, 18.5% in the placebo group). Although most of these were in the range of 20 – 30 µ/L, five patients in the ramelteon group had an increase > 40 µ/L, compared to one patient in the placebo group. Based on these data alone, causality is difficult to definitively establish; however, there is published literature indicating an association between melatonin levels and prolactin elevations. Due to this possible association, continued evaluation of ramelteon's effect on prolactin levels, and its long-term consequences on bone metabolism and reproductive health should be considered.

Study TL022

TL022 is a12-month, open-label, uncontrolled, fixed-dose study. Patients were assigned to either 8 mg of ramelteon (=65 years of age), or 16 mg of ramelteon (18 – 64 years of age). For purpose of data analyses, they were categorized into one of the following:

- 24-week compliant: subjects who had taken an average of = 3 doses/week during the first 24 weeks of the study
- 48-week compliant: subjects who had taken an average of = 3 doses/week during the first 48 weeks of the study

It is important to note that due to a high dropout rate, the majority of the patients had study medication exposures of < 32 weeks; only 77 patients had a total drug exposure of 48 weeks or greater.

With respect to the findings, the incidence of abnormal thyroid function studies was comparable to what was observed in the other two studies, and may be reflective of the background rate of thyroid dysfunction. There were two patients (0.16%) with abnormal morning cortisol levels who subsequently were evaluated with ACTH stimulation testing and were found to be abnormal. There were no patients in the two controlled studies who had abnormal ACTH stimulation tests. There was a decrease in the mean Total and Free testosterone levels noted in the 8 mg dose group from baseline to Months 4 and 8, while the 16 mg group had a slight increase in mean testosterone levels over time. Without a placebo group, it is not possible to discern the significance of this finding.

The overall conclusion based on the data available to date is that the number of patients, and the duration of exposure are insufficient to exclude the possibility that ramelteon is associated with chronic hyperprolactinemia. However, due to the fact that prolactin levels can increase for a variety of reasons, routine monitoring of prolactin levels is not recommended while on ramelteon therapy, but should instead be considered as part of the focused clinical evaluation in someone who presents with amenorrhea or sexual dysfunction.

Pediatric patient population
The applicant had originally requested a deferral of pediatric studies during the Pre-NDA meeting. These studies should be deferred until ramelteon's impact on the endocrine system is better evaluated.

Scheduling recommendation
Based on review of the data from abuse liability studies submitted by the applicant, the Controlled Substances Staff is proposing that ramelteon not be controlled under the Controlled Substances Act. This recommendation is usually not incorporated into the decision-making process regarding the approvability of a product; however, it is important to be cognizant of the potential ramifications that, if approved, ramelteon would represent the first unscheduled hypnotic. It is highly probable that such a classification would result in different prescribing patterns, with the potential for greater patient exposures to ramelteon than other hypnotics.

Recommendations
The applicant has conducted a significant number of studies in the course of the development of ramelteon. They have been interactive with the Division at the appropriate junctures in their application. However, after approximately 3500 patients being exposed to ramelteon in various studies, the final assessment is that ramelteon has a statistically significant treatment effect that is of marginal clinical significance.

In addition to the findings that the treatment effect does not seem robust, either in the form of additional analyses, or in the case of some of the secondary efficacy endpoints, there is the observation that that ramelteon fails to demonstrate a treatment effect in the subjective efficacy parameters. The applicant proposes that ramelteon's unique mechanism of action makes it difficult for patients to appreciate the shortened LPS and increased TST provided, and the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than benzodiazepine receptor agoinist. Although the applicant's proposal may be true, at this point it appears to be more speculative and not supported by any data. Furthermore, even if the applicant is correct, the end result is the same in that the patients who are currently being targeted by the proposed indication do not seem to recognize any benefit from treatment with ramelteon.

Ordinarily, a marginally clinically significant treatment effect would not preclude an approval of a product. However, the ability to approve such a product would then focus even more on the safety profile, as the risk:benefit assessment is being made.

In the case of ramelteon, there are several issues in the safety profile that are of concern. First is the observation that a significant portion of patients experienced one type of adverse event or another, highlighting that ramelteon is not an entirely benign product. Secondly, there is the observation that there appeared to be a number of patients who experienced hyperprolactinemia. Due to the number of patients exposed and the duration of exposure, it is not possible to determine whether there was a true causal relationship; however, it is also not possible to definitively exclude a relationship between the hyperprolactinemia and ramelteon therapy. Third, there is the positive result in one of the *in vitro* chromosome aberration genetic toxicology studies. It is acknowledged that several other assays were negative, and it may possible that this result actually represents an erroneous finding, however, this still needs to be addressed to determine whether ramelteon is truly a genotoxic carcinogen. Lastly, the pharmacokinetic findings that indicate a large inherent *in vivo* variability and potential for drug-drug interaction portend potential difficulties in the general population.

These concerns could potentially be handled in the labeling of the product, with appropriate information, advice, and/or warning language that would help the prescriber use ramelteon most appropriately. However, that presupposes that ramelteon offers something to the patient population being proposed by the applicant. The applicant has not submitted sufficient data to support that position.

My recommendation is that the current application be deemed "Approvable." In order for this application to be approved, the applicant will be required to either identify a patient population in which the treatment effect demonstrated by ramelteon is not only statistically significant, but also of significant clinical significance to outweigh the currently known risks of ramelteon. Alternatively, the applicant can provide sufficient information to put the currently known risks of ramelteon into perspective. This would include further elucidation of the relationship of ramelteon therapy and hyperprolactinemia, and re-assessment of the positive result in the genotoxicity assay.

Depending on the additional information submitted, a decision can then be made as to whether the risk:benefit profile would support approval of ramelteon.

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/s/

Rigoberto Roca
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MEDICAL OFFICER

CLINICAL REVIEW

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Established Name	Ramelteon
(Proposed) Trade Name	[illegible]
Therapeutic Class	Hypnotic
Applicant	Takeda
Priority Designation	S
Formulation	Tablet
Dosing Regimen	One tablet nightly
Indication	Insomnia
Intended Population	Adults with primary insomnia

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approval action for this product.

The sponsor has suggested the following wording, "[Ramelteon] is indicated for the treatment of insomnia. [redacted] The sponsor's primary goal was to demonstrate that ramelteon increased the duration of sleep by decreasing sleep latency using PSG measurement of latency to persistent sleep as well as subjective measures of time to sleep onset. There is objective evidence that this product decreases the latency to persistent sleep for up to 35 days of therapy. There is inconsistent subjective evidence that this product does so. I can concur that this product has an immediate hypnotic effect and may appropriately be used in the short-term treatment of insomnia.

Though I am recommending ultimate approval of this product, I would like to make some comments regarding efficacy as well as the pharmacotoxologic findings.

Efficacy
Insomnia is an interesting disorder as it is one of the few conditions with objective and subjective means of measuring the same endpoint. Both objective and subjective measurements are important for this condition, and the case could be made that from a clinical standpoint, the subjective measures are perhaps more important. As we realize that insomnia has both a physiologic and a psychiatric component, it is important that a proposed hypnotic demonstrate objective (e.g. sleep laboratory PSG) and subjective (e.g. outpatient sleep diaries) evidence of efficacy. Upon realization that the outpatient study (TL020) in adults had failed to demonstrate efficacy on the primary endpoint, the company proposed the following explanatory hypotheses: 1) the novel mechanism of action of their product makes it difficult to appreciate the shortened LPS and increased total sleep time (TST) provided and 2) the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than the efficacy of the benzodiazepine receptor agonists. Unlike an anti-hypertensive or a cholesterol lowering agent, in which the patient is reliant upon the clinician's assessment of the objective lab data in order to determine efficacy, in this case the patient's subjective determination of effectiveness or lack thereof will not be negated by the fact that there is or isn't objective evidence of efficacy. This product appears to have a subtle mechanism of action that makes it difficult for the end-user to appreciate its' beneficial effects.

Pharmacotoxologic findings
During preclinical development, one of the chromosomal aberration assays was found to be positive. Additionally the rate of hepatic tumors seen in rodent models was higher than might have been expected. Although, even when taken together, these findings in the absence of human correlation do not preclude approval, they do suggest that this product bears careful scrutiny in

the first 24-36 months post-approval when it will almost certainly be used in healthy females of child-bearing potential. As the product moves into a wider market, I would suggest that the company set up a pregnancy registry with mandatory reporting incorporated into the annual report to the Agency so that both Takeda and the FDA may be alerted about patients who become pregnant while on medication and any potential adverse events that might arise during those pregnancies.

The possible relationship between this product and neoplasms in rodents is also an area of concern. While the rate of neoplasia was very low during the clinical trials portion of the development program, the sample size was small. It would behoove Takeda and the Agency to monitor the post-marketing adverse events for evidence of an increased rate of neoplasms in humans, with hepatic, pituitary and mammary gland tumors being of particular interest. Having said that, I acknowledge the difficulty of teasing out potential causality with respect to mammary gland tumors since the latter are frequently seen in women who are not taking any medications.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no recommended risk management activity for this product.

1.2.2 Required Phase 4 Commitments

[

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1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests for this product.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ramelteon, a new molecular entity (NME), is a selective MT_1 and MT_2 receptor agonist. Sleep promotion in humans is thought to be affected by the binding of melatonin to MT_1 and MT_2

receptors in the suprachaismatic nucleus (SCN). The SCN normally produces an alerting signal, which promotes wakefulness. Melatonin, which is produced in response to the absence of light, is hypothesized to attenuate that alerting signal and promote sleep. The homeostatic mechanisms are responsible for balancing sleep load; when one has a high sleep load, one sleeps. During sleep the sleep load lessens; when it has reached an appropriate level, one awakens. The alerting signals produced by the SCN in response to circadian rhythm are superimposed upon the homeostatic mechanisms.

The sponsor performed over forty studies during the development program for this product; seven of which were designed to evaluate efficacy. Two studies, PNFP002 and TL023, were randomized, double-blind, placebo-controlled, single dose studies performed in adults using a transient insomnia model. TL005 was a randomized, double-blind, placebo-controlled, crossover dose response study performed in healthy adults with chronic insomnia. TL017 was a randomized, double-blind, placebo-controlled, crossover study performed in elderly patients with chronic insomnia. TL020 was a randomized, double-blind, placebo-controlled, fixed-dose outpatient study performed in healthy adults with chronic insomnia. TL021 was a randomized, double-blind, placebo-controlled, fixed-dose study performed in healthy adults with chronic insomnia which used polysomnographic measurement of sleep latency as well as subject diaries and questionnaires to assess subjective time to sleep onset. TL025 was a randomized, double-blind, placebo-controlled, fixed-dose study performed in elderly patients with chronic insomnia which used subject diaries to assess subjective time to sleep onset.

Two long term safety studies, TL032 (6 months) and TL022 (12 months), were performed to evaluate the possible endocrine effects of ramelteon.

The sponsor has proposed that ramelteon be indicated for the treatment of insomnia in persons 18 years of age and older. The suggested dosing regimen is 8 mg taken by mouth within 30 minutes before going to bed.

The proposed trade name for this hypnotic was [redacted] After the approval of the hypnotic Lunesta (eszopiclone) in December 2004, Takeda was informed that they would have to select an alternate trade name to avoid confusion.

1.3.2 Efficacy

The sponsor's primary goal was to demonstrate that ramelteon decreased sleep latency as evaluated by objective measures, i.e. polysomnography, and as evaluated by subjective measures, i.e. sleep diaries/questionnaires.

While study TL023 did not replicate the finding of efficacy for the 16 mg dose previously demonstrated in PNF002, it did objectively demonstrate, using a sleep laboratory model of transient insomnia, that a single 8 milligram dose would decrease sleep latency in healthy adults.

In all of the chronic insomnia studies which used objective measures of sleep latency, ramelteon was demonstrated to decrease sleep latency at all doses studied for the first 7 days of treatment.

In one of the studies, TL025, which used subjective measures to evaluate time to sleep onset, using an analysis of means the sponsor found an immediate and a persistent effect of ramelteon. Neither the sponsor's responder analysis nor the responder analysis done by Dr. Price supported this finding.

The effect of ramelteon was maintained through the 35-day study period as determined by the analysis of means performed by the sponsor on studies 021, which used objective measures as the primary means of evaluation, and 025, which used subjective measures as the primary means of evaluation. In Dr. Price's responder analyses of these same studies, the effect of ramelteon was not maintained over the 35-day period. The sponsor's responder analysis also failed to demonstrate that an effect was maintained over the 35 day period.

While the sponsor was able to provide objective evidence of an immediate effect on sleep latency, there is a paucity of the expected subjective support. Even in trials where there was clear objective evidence of a decrease in sleep latency, the subjective determinations of total sleep time and sleep quality did not mirror the objective findings.

The results from sub-group analyses by gender, age, or ethnicity were inconsistent across studies.

1.3.3 Safety

There were two deaths reported during this clinical development program: both were patients who were struck by motor vehicles.

There were multiple SAEs reported during development including a prolactinoma. The labeling for this product will include an instruction to the practitioner to evaluate prolactin levels in the face of unexplained amenorrhea.

The most frequently reported treatment emergent adverse events (TEAE) during this development program were headache, next-day somnolence, nausea and dizziness.

In general, no statistically significant next-day residual effects on objective measures or on subjective measures were seen. In a single study, patients who received 8 mg had a worse delayed recall score and a worse immediate recall score at week 3. In this same study, subjects felt more fatigued at week 1 and more easily irritated/more sluggish at week 3.

1.3.4 Dosing Regimen and Administration

The sponsor recommends that adult patients with chronic insomnia take a single eight milligram tablet of ramelteon within 30 minutes of bedtime. During the sleep laboratory components of the development program, ramelteon was administered on the proposed schedule. The pharmacokinetic data demonstrated that the peak levels of ramelteon occurred between 30 minutes and 90 minutes after dosing.

The sponsor notes that while doses of 4 to 64 milligrams were studied and shown to be efficacious in their analysis, the 8 milligram dose appeared to give the most consistent results. It is noted that no consistent efficacy dose-response correlation was ascertained during the development program.

When ramelteon 16 mg was administered to fasting healthy adults, an approximately 50-fold difference in C_{max} between minimum and maximum values for a given individual and an 80-fold difference in AUC between minimum and maximum values for a given individual were noted. Due to this change in absorption with food, we will recommend that this product not be taken with food.

A two fold difference in AUC was found when elderly subjects were compared with adults; the sponsor concluded that a dose adjustment based upon age was not necessary in light of the wide intersubject variability. Our internal review did not concur with that assessment; we will recommend a reduction to 4 mg as the starting dose for the elderly.

1.3.5 Drug-Drug Interactions

Ramelteon does not inhibit the CYP2D6 isozyme. No dose adjustments are recommended when ramelteon is concurrently administered with CYP2C9, CYP2C19, CYP2D6, CYP3A4 inhibitors. No dose adjustments are needed when ramelteon is co-administered with theophylline or other CYP1A2 substrates.

The sponsor advises caution when ramelteon is used together with a CYP1A2 inhibitor though no specific dose adjustments are advised. We would strengthen that recommendation to state that the two should not be used concomitantly.

This product will [redacted] and should be used cautiously by patient with renal impairment.

The sponsor advises caution when this medication is used with ethanol. We would strengthen that recommendation to state that the two should not be used concomitantly.

1.3.6 Special Populations

Gender
There is no consistent evidence that gender has an effect on the safety or efficacy of this product.

Age
There is no consistent evidence that age has an effect on the safety or efficacy of this product, however a subgroup analysis of adverse events by age did reveal that the proportion of the elderly who complained of anorexia, depression, and myalgia was higher than that of the non-elderly adults.

Ethnicity
There is no evidence that ethnicity has an effect on the safety or efficacy of this product.

Hepatic impairment
This product is [redacted] for patients with hepatic impairment.

Renal impairment
We recommend that this product be used cautiously in patients with [redacted] type of renal impairment.

COPD, Sleep apnea
The sponsor is not recommending dose adjustment of ramelteon for patients with mild to moderate COPD or sleep apnea.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ramelteon, a new molecular entity (NME), is a selective MT_1 and MT_2 receptor agonist. Sleep promotion in humans is thought to be affected by the binding of melatonin to MT_1 and MT_2 receptors in the suprachaismatic nucleus (SCN). The SCN normally produces an alerting signal, which promotes wakefulness. Melatonin, which is produced in response to the absence of light, is hypothesized to attenuate that alerting signal and promote sleep. The alerting signals produced by the SCN in response to circadian rhythms are superimposed upon the homeostatic mechanisms. The homeostatic mechanisms are responsible for balancing sleep load; when one has a high sleep load, one sleeps. During sleep the sleep load lessens; when it has reached an appropriate level, one awakens. [Borbely 1982; Brzezenski 1997; Edgar 1993; Liu 1997; Monti 2000; Turek 2001; Vgontzas 2002]

The proposed trade name for this hypnotic was [ ] After the approval of the hypnotic Lunesta (eszopiclone) in December 2004, Takeda was informed that they would have to select an alternate trade name to avoid confusion.

The sponsor has proposed that Ramelteon is indicated for the treatment of insomnia in adults including the elderly. The suggested dosing regimen is 8 mg within 30 minutes of going to bed.

2.2 Currently Available Treatment for Indication

Currently there are four FDA approved products indicated for the short-term treatment of chronic insomnia: Halcion (triazolam); Prosom (estazolam); Ambien (zolpidem); Sonata (zaleplon). Lunesta (eszopiclone) is approved for the treatment of chronic insomnia but its' indication does not limit it to short term use.

A number of other products are used off-label to treat chronic insomnia, e.g. tricyclic antidepressants, anxiolytics, and antihistamines.

2.3 Availability of Proposed Active Ingredient in the United States

This product represents a new molecular entity which is not currently marketed.

2.4 Important Issues With Pharmacologically Related Products

There have been no labeling changes in association with the approved hypnotics due to safety or effectiveness concerns. While most of the approved hypnotic products contain language stating that the product is meant for short-term treatment of insomnia, that language was removed from the eszopiclone label on the basis of studies submitted in support of that NDA.

The safety concerns associated with the currently-marketed hypnotics include next-day residual effects as well as neuropsychiatric adverse events such as confusion, amnesia, hallucinations, and worsening of psychiatric disorders, especially when the medications are not taken immediately before bedtime. The next-day residual effects on attention and vigilance are usually evaluated during the development plan for drugs in the sedative/hypnotic group. Some sponsors are beginning to develop methods to specifically evaluate next-day driving ability. The known neuropsychiatric adverse events are predominantly handled through labeling. The labels for these drugs all specify that the drug is to be taken at bedtime. When people do not take the drug immediately before bed, they may experience confusion as well as lacunar amnesia for their actions between ingestion of the pill and actually falling asleep.

2.5 Presubmission Regulatory Activity

November 8 2001, EOP1 meeting

[*Reviewer's note: I have elected to focus on that part of the discussion which is relevant to the insomnia indication under current review. This product was originally referred to as TAK-375 but later the sponsor began referring to it as ramelteon. Both names may be found in the body of this review.*]

The main topic of discussion was the development program for this product, specifically the components needed to achieve [redacted] an insomnia indication [redacted]

The following key points were made during that discussion:

- The Agency agreed that six months of efficacy data from a single placebo-controlled trial in patients with chronic insomnia would be sufficient to support long-term (up to 6 months) administration of [ramelteon], if accompanied by appropriate safety data.
- The Agency agreed that an enrollment of approximately 2000 participants, with 300 to be studied for at least 6 months and 100 to be studied for at least 12 months would be acceptable as long as no safety signal were to be detected.
- The Agency stated that drug discontinuation effects would have to be assessed in both a four-week sleep lab study and a six month chronic insomnia study.
- The Agency agreed that the six abuse liability studies proposed were acceptable and noted that the studies should include low, medium and high doses with the high dose being 2-3 times higher than the highest proposed therapeutic dose.
- Representatives of the Agency's Office of Clinical Pharmacology and Biopharmaceutics (OCPB) noted the variability in [ramelteon] pharmacokinetics and emphasized the importance of integrating the attributable factors, exploring the exposure-response relationships and defining optimal dosing strategy for the "subgroups and individuals in the target patient population. Population approach...should be considered where appropriate. In addition, the plan should also incorporate the following: M-II, the active metabolite and major circulating moiety, and potential additive effect to the PK of [ramelteon] from major attributable factors to the PK variability." OCPB recommended

that the sponsor incorporate the following considerations into the development plan: the relative importance of isoenzymes including CYP2C9, 3A4 and 1A2 to the overall metabolic fate of TAK-375, the potential impact of a CYP2C9 enzyme polymorphism on the PK and response of TAK-375, exploration of the ethnic difference of CYP2C9 activity in the metabolism of [ramelteon], incorporation of the relevant information into studies exploring PK and PK/PD relationship of [ramelteon].

July 16 2002, EOP2 meeting

Takeda presented the proposed development plan which consisted of 2 chronic insomnia studies in adults (studies 020 and 021), 2 chronic insomnia studies in the elderly (studies 017 and 025), 2 transient insomnia studies in adults (studies 002 and 023) and one long-term safety study (Study 022). The proposed indication was the treatment of insomnia, both transient and chronic.

- FDA response: The program is acceptable for this indication.

Takeda stated that they had completed one transient insomnia study with 16 mg and 64 mg of TAK-375, using a first night sleep lab model of transient insomnia, and planned a confirmatory study using the same model but using doses of TAK-375 8 MG, 16 mg or placebo. Takeda wished to know if the aforementioned studies would suffice in support of the proposed labeling provided in Section 2.0 of the briefing document.

- FDA response: It would be unusual to mention the results for the various specific outcomes (i.e. latency, total sleep time, sleep efficiency and number of awakenings, in the Indications section of the label. The focus in [Indications] is generally on the two important clinical questions, i.e. sleep onset —— The data supporting claims in those two areas would more appropriately be included in clinical trials. It was noted that the statistical plans for these studies would need to address multiple endpoints if they intended to get this information into [the Clinical trials section of the label.] We encouraged [the sponsor] to limit their focus to two measures, i.e. sleep latency to support an onset claim and WASO to support —— claim.

Takeda indicated that based upon their Phase II studies, they had elected to study doses of 8 mg and 16 mg in the adult population with chronic insomnia and doses of 4 and 8 milligrams in the elderly population with chronic insomnia. The lower doses in the elderly were based upon pharmacokinetic differences seen in an age/gender study.

- FDA response: Consider testing the 4 mg dose in adult non-elderly patients since that dose did seem to have some clinical activity. This is a recommendation not a requirement but the data could be of importance if dose-related toxicity were noted.

Takeda stated that the primary efficacy parameter in each of the placebo-controlled Phase III studies would be sleep latency. The four studies which included PSG assessments (005, 021, 017, and 023) would define the primary endpoint as PSG-based latency to persistent sleep. The studies that did not include PSG assessments would define the primary endpoint as the patient's assessment of the time to sleep onset. For all three studies in chronic insomnia the primary efficacy assessment was to be performed using the average of the sleep latency assessments

during the first week of double-blind treatment (average of day 1-2 for the sleep lab studies and average of day 1-7 for the outpatient studies).

The maintenance of the therapeutic effect over the 35-day treatment period was to be assessed by analysis of average sleep latency during week 5 of treatment. The analysis was to use observed data as well as data imputed using LOCF. Separate analyses of the intermediate weeks were also planned. The type I error rate was to be controlled using Dunnet's procedure for the primary analysis of the week 1 average sleep latency as well as the secondary analyses of the other timepoints.

- FDA response: Sleep latency is an acceptable primary outcome to support a claim for reduction in sleep onset. We encouraged [the sponsor] to consider WASO as a key secondary outcome to support a claim [ ]. We noted that other proposed secondary endpoints, i.e. TST and sleep efficiency, were not ideal and would likely not be acceptable for supporting a [ ] claim.

  We agreed that it would be appropriate to begin the [primary efficacy] analysis with week 1 data. We noted that the overall statistical plan was problematic for the standpoint of controlling Type I error. We strongly encouraged them to develop and resubmit a detailed statistical plan that addressed the primary and ideally one key secondary outcome (WASO), the two doses, and the sequential analysis of multiple timepoints. We noted that it would be problematic if they had positive results at early and late timepoints but negative results at the intermediate timepoints.

Takeda indicated that withdrawal effects were to be assessed using a single-blind placebo run-out period at the end of each of the 35-day chronic insomnia studies. The Tyrer benzodiazepine withdrawal symptom questionnaire (TBWSQ) was to be performed at baseline and at each visit during the double-blind treatment and the single-blind placebo runout. A withdrawal effect was to be defined as the onset or worsening of at least 3 symptoms from a prior assessment. Withdrawal symptoms were to be assessed separately for each day of the single-blind placebo run-out period.

- FDA response: We indicated that our preference would be for comparison of drug to placebo on mean change for the TBWSQ from the last day on treatment in the total score on days 1 and 2 off treatment separately.

Rebound insomnia effects were to be assessed using a single-blind placebo run-out period at the end of each of the 35-day chronic insomnia studies. Sleep latency will be collected daily during the single-blind run-out period. Rebound insomnia was to be defined as sleep latency recorded during the single-blind placebo run-out at least six minutes greater than the largest sleep latency recorded during the baseline. Rebound insomnia will be assessed separately for each day of the single-blind placebo run-out period.

- FDA response: We asked for an analysis similar to the one to be used for assessing withdrawal, except using a comparison with change from initial baseline scores.

Other issues raised by HFD-120 at this meeting were:

- The need for monitoring of endocrine parameters in long-term safety studies. Drs. Chou and Uppour indicated that an effect on human testosterone levels had been seen in the EC002 study. Changes in serum testosterone and T4 had been seen in non-clinical reproductive and hormone studies in the rat (study M-11-0073 and others).
- Pharmacokinetic concerns
    - The effect of the induction of CYP3A4, 2C9 and 1A2 on the PK/PD of [ramelteon]. Those isozymes are the primary pathways for metabolizing [ramelteon] to M-II (an active metabolite within the plasma) and M-IV.
    - A drug interaction study with rifampin may be clinically relevant and should be considered since [ramelteon] is known to be metabolized through CYP3A4, 2C9 and 1A2.
    - The proper omeprazole dose should be used to investigate the induction of CYP1A2 and its effect on the PK/PD of TAK-375 since omeprazole exhibits dose-dependent inhibition/induction of P450s.
    - Significant food effect was observed with light breakfast finished 10 minutes prior to the dosing. FDA recommended that future studies be conducted in a fasting state or the sponsor should document any food intake and time relative to study drug administration and incorporate these into covariate analysis. This information may also inform the labeling for special populations.
    - Investigations of the ethnic effect on PK/PD of [ramelteon] and the underlying mechanism of observed ethnic difference in PK of [ramelteon] and metabolites.
    - Investigations of the relative importance of the functionally polymorphic CYP2C9 in the elimination of [ramelteon] since significant interethnic differences exist in CYP2C9 enzyme activity and the allele prevalence. The sponsor indicated that the race-effect will be investigated in Phase III trials. In order to full investigate this effect, sufficient subjects of various races should be recruited in these trials.
    - The agency would like to see population PK analysis performed using intrinsic and extrinsic relationships as covariants during Phase III.

      Takeda responded to this last issue in supplement 062 to their IND (24 Sept 02)- stating that since the elimination half-life of [ramelteon] and M-II are short, it would be impractical to draw bloods for population PK analysis 6-8 hours after drug ingestion. The sponsor stated their intention to assess the effects of covariates such as age, gender, body weight, race, liver function, renal function either from meta-analysis of various PK studies or from special population PK studies.

FDA agreed that it would be acceptable to give safety data for 300 patients followed for 6 months at the time of NDA submission followed by the data for 100 subjects followed for 12 months at the time of the 120 day update.

FDA agreed that it would be acceptable to omit a separate performance study assuming that there continued to be no consistent changes in the digit symbol substitution test (DSST), the word memory recall test or subjective measurements of alertness upon awakening.

FDA agreed that the proposed drug-interaction study with St. John's wort (a CYP3A4 inducer) was acceptable but suggested that rifampin be used instead.

FDA agreed that if no notable evidence of QT prolongation was seen in studies EC002 and EC003, a formal ECG study would not be required.

In response to Takeda's request for a deferral of the pediatric study requirement, the FDA responded that the Division (HFD-120) has been granting waivers for the sedative/hypnotics based upon the Pediatric Advisory Committee recommendations.

November 20 2002

A teleconference was held to discuss monitoring on endocrine functioning in the Phase III development program for [ramelteon]. Takeda had noted both during previous teleconferences as well as during the EOPII meeting in July 2002, that [ramelteon] had the potential to impact human endocrine function.

Three clinical trials were proposed to provide data on the extent of the effect of [ramelteon] on human endocrine function. Takeda stated that they planned to provided the final results of the endocrine monitoring for both a long-term safety study (TL-375-022) and a long-term endocrine study (TL-375-032) at the time of the 120-day safety update. Dr Katz (Division director of HFD-120) replied that while the Agency would make every effort to review the data in a timely fashion but the Agency could not guarantee that the review would be completed prior to the first PDUFA action date.

1. TL-375-031: A four-week, placebo-controlled clinical study to assess any potential short-term effects of TAK-375 [ramelteon] on endocrine function in 100 healthy adult volunteers
   Endocrine parameters were to be monitored at baseline, after 2– and 4- weeks of daily dosing, and again 2 weeks post-study:
   - Both genders: T_4, free T_4. T_3. TSH, LH, FSH, ACTH, AM cortisol, prolactin
   - Males: Free and total testosterone
   - Females: Estradiol

2. TL-375-032: A six-month, placebo-controlled clinical study to assess any potential longer-term effects of TAK-375 [ramelteon] on endocrine function in 120 adults with chronic insomnia
   Endocrine parameters were to be monitored at baseline, after 1-, 2-, 3-, 4-, 5- and 6-months of daily dosing, and again 2 weeks post-study:
   - Both genders: T_4, free T_4, T_3, TSH, LH, FSH, ACTH, AM cortisol, prolactin
   - Males: Free and total testosterone

- Females: Estradiol; LH surge testing was to be done during months 1-, 2- ,3-, 4- 5-, and 6 on pre-menopausal women who were not using contraceptives. Menstrual history was to be documented at baseline.
- ACTH stimulation testing was to be conducted at baseline and at the final study visit for a subset of approximately 50 subjects (25 active group; 25 in the placebo group)

3. TL-375-022: A long-term open-label safety study of TAK-375 [ramelteon]
    - Both genders were to have the following parameters monitored at baseline, after 1-, 2-, 4-, and 8-months of daily dosing, and again at the final visit: T_4, free T_4. T_3. TSH, AM cortisol
    - Males: Free and total testosterone was to be obtained at baseline, after 1-,2-,4-,and 8-months of daily dosing, and again at the final visit; LH, FSH were to be obtained at baseline, after 4 months of daily dosing, and again at the final visit
    - Females: Menstrual diaries were to be kept for the duration of the study

The sponsor proposed to analyze the data from this study cohort in its entirety as well as doing a subset analysis by dividing the participants into groups of people with normal baseline endocrine values and those without. Subjects who were known to have confounding medical conditions and those who were known to be taking medications that could affect endocrine function would also be reviewed in a subset analysis.

Takeda agreed to provide a report of any abnormal endocrine findings in patients who had completed 4-, 8- and 12 months of therapy. Takeda also planned the following response for newly detected endocrine abnormalities:
Changes in primary outcome variables, defined as T_4, free T_4, T_3, TSH, free or total testosterone, were to be treated as a new laboratory abnormality and appropriate medical intervention by the investigator was expected.

- Participants with new abnormalities in testosterone levels were to have a re-evaluation of testosterone along with the gonadotrophins at the "earliest practical point."
- Values of AM cortisol <7.5 micrograms/dl were to be reported to the Agency as a significant adverse event. Appropriate endocrine evaluations and treatments were to be instituted by the clinical investigator.
- Values of AM cortisol between 7.5 and 10 micrograms/dl were to be evaluated and treated as a standard adverse event. If appropriate endocrine evaluations confirmed the diagnosis of adrenal insufficiency, the Agency was to be notified at the "earliest practical point."

February 11 2004

A teleconference was held, at Takeda's request, to provide guidance for the then ongoing development plan. Takeda had positive results in the inpatient setting but a failed result in the one completed outpatient study, study 020. The results from the second outpatient study, study 025, were pending.

Takeda had submitted the following questions in a meeting briefing package:

1. Are subjective data obtained only in the inpatient (sleep laboratory) environment, using the post-sleep questionnaire, sufficient to document positive patient reported efficacy, together with the PSG data?
    - FDA response: Subjective data obtained only in an inpatient environment using the post-sleep questionnaire together with objective polysomnography (PSG) data will not suffice to document positive patient reported efficacy.
2. If the answer to the first question is yes, need these subjective assessments of efficacy be a pre-specified endpoint? If these endpoints must be specified a priori, need they be identified as primary endpoints?
    - FDA response: This question is not applicable based upon the response to the first question
3. If both inpatient and outpatient subjectively reported efficacy is required, would the following combination of data be acceptable evidence of efficacy:
    a. Clinically meaningful and statistically significant improvement in LPS and TST versus placebo using PSG
    b. Statistically significant improvement versus placebo using responses to post-sleep questionnaires in the sleep laboratory
    c. Supportive findings in patient reports of efficacy at home which may or may not achieve formal statistical significance
        - FDA response: The proposed combination would not be acceptable.

The Division (HFD-170) made the following general comments:
A drug for chronic insomnia should demonstrate efficacy in a real world setting, i.e. outpatient. The Division noted the sponsor's hypothesis that the novel mechanism of action of their product makes it difficult to appreciate the shortened LPS and increased total sleep time (TST) provided by ramelteon. The Division also noted the sponsor's hypothesis that the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than benzodiazepine receptor agonists. The Division stated that the sponsor should develop an outpatient study that demonstrates efficacy while taking into account the unique properties of the product. The sponsor stated that study 025 (elderly, outpatient study) is identical to failed study 020 (adult outpatient) study and inquired whether study 025 would be acceptable [in support of approval] if it met its primary objective. The Division stated that it might be possible to extrapolate efficacy to the younger population based upon the results of study 025 but this would depend upon the results of the study. The sponsor inquired about clinical global impression (CGI). The Division stated that they would be willing to consider this as a secondary endpoint.

June 22 2004 Pre NDA meeting

[*Reviewer's note: In the interest of brevity, I have omitted the questions/responses that concerned issues related to the electronic filing techniques to be used.*]

Takeda informed the Agency of its intent to utilize the data from primary efficacy trials 017, 021, 023 and 025 and supportive trials to support the following proposed indication: [redacted]

Administrative

Takeda …intends to seek a "P" designation for the review of the NDA. Does the Agency concur that this is a reasonable request?

- FDA response: We do not concur with the priority designation. We agree that the mechanism of action is novel but we are not convinced that ramelteon eliminates or substantially reduces specific treatment limiting drug reactions.

Takeda is planning to request a deferral of the requirement to conduct insomnia studies in the pediatric population…does the agency agree that a deferral of the requirement for pediatric studies is acceptable?

- FDA response: We will grant a deferral. Since ramelteon has a novel mechanism of action, we would prefer to have postmarketing safety data from adults before commencing studies in children.

Pharmacology/Toxicology

The database for nonclinical studies of ramelteon and its principal active metabolite MII is listed in the proposed CTD table of contents, Module 4 (appendix D). Do the listed studies support this NDA filing?

- FDA response: As discussed in the CMC pre-NDA meeting of 12/15/2003, quantification of several isolated impurities in two *in vitro* genetic toxicology assays is still required and should utilize concentrations that produce cytotoxicity or reach the upper concentration limit specified in ICH S2A Guidance. With this exception, the studies listed appear to satisfy the nonclinical study requirements for the filing of an NDA. The Division clarified that if the specifications were tightened to [ ] then no studies would be needed. However, the Division stated that this specification holds for structures that do not contain any structural alerts for mutagenicity. If the structures suggest the potential for increased toxicological risk, the qualification threshold may need to be reduced to [ ] level.

Are the nonclinical studies adequate to support the proposed labeling and chronic use of this compound?

- FDA response: The chronic use studies conducted in rat and monkey are sufficient to support a chronic duration of use. The support for dosing and overall adequacy of these studies will be a review issue.

Mechanistic evaluations for the Hardarian, liver and Leydig cell tumors observed in the 24-month rodent carcinogenicity studies are included in the nonclinical profile for ramelteon. Are these evaluations adequate to support the proposed labeling?

- FDA response: The adequacy of the mechanistic studies to describe the relevance/non-relevance of the positive carcinogenicity results to human is considered a review issue and will be assessed as part of the NDA review. Support for the proposed labeling will depend upon the Division's assessment of the explanation submitted by the sponsor and the quality and thoroughness of the

mechanistic studies provided. Input will be sought from the Executive Carcinogenicity committee to determine if they concur with the mechanistic explanations proposed.

Additional FDA pharmacology/toxicology comments:

- Provide a justification for the adequacy of dose selection for both rat and mouse carcinogenicity bioassays as protocol concurrence from the Executive Carcinogenicity Assessment Committee was not obtained. This justification should take in to account and reference the ICH guidelines for dosing in carcinogenicity studies.
- Provide a metabolite comparison between nonclinical species and humans which delineates the exposure margins in nonclinical species of observed human metabolites.

Human Pharmacology

Takeda does not plan to include a CYP1A2 class restriction on ramelteon based upon the drug-drug interaction data. Does the Agency agree?

- FDA response: The Agency [was] unable to agree…pending thorough review and understanding of this data and the risk/benefit ratio of the drug.

Clinical

…Takeda proposes to remove the following elements considered 'class labeling' of sedative-hypnotics that are not applicable to ramelteon.
-Hypnotics should generally be limited to 7 to 10 days of use and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks
-[Hypnotics] should not be prescribed in quantities exceeding a 1-month supply
-A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative-hypnotics
It can rarely be determined with certainty whether a particular instance of the abnormal behaviors described above is drug-induced…
Following the rapid dose decrease or abrupt discontinuation of sedative hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs
Does the agency agree that removal of these portions of class labeling is appropriate?

- FDA response: We will be willing to modify the labeling if the provided data is supportive of our doing so.

Do the data provided adequately justify the dose recommendation for adults and the elderly?

- FDA response: While the data appears to be adequate, this is a review issue. As an example, it is noted that the incidence of adverse effects was lowest in the group which took more than 16 mg, though this may be an artifact of the small sample size…It is also noted that in the transient insomnia model, latency to persistent sleep (LPS) seemed to increase with higher doses. A detailed review of the study data will allow us to determine whether we concur with the choice of dose.

Abuse liability

Are the abuse, dependency and withdrawal data in the NDA sufficient to support a non-scheduled status for ramelteon?

- FDA response: An NDA submission should include primary data and full methodologies, including doses of ramelteon that were utilized in the animal and human studies. Additionally, a full binding profile should be submitted in the NDA abuse potential package.

120 day safety update

Will the Agency accept the final clinical study report [for study 01-02-TL-375-022] at the 120 day safety update? We note that the Agency will have reviewed up to 9 months of endocrine data from study 022 prior to the 120-day safety update.

- FDA response: It is OND policy that the application should be complete at the time of submission. Since the potential endocrine effects are an important part of the safety evaluation, we will expect the final study reports for all of the endocrine studies as part of the initial NDA submission. In response to the sponsor's assertion that study 022 was a confirmatory study which should not be required for submission in the original NDA, the Division stated that the best regulatory pathway for a first cycle approval would be to include [a final study report] for study 022 with the initial NDA. However, if the sponsor felt confident that the safety and efficacy findings for study 032 would be sufficient for a complete review package, then the sponsor would not need to include study 022...the Division noted that might not reach the same conclusion about the safety findings as the sponsor did.

Based upon a commitment made at the EOP2 meeting on 16 July 2003, the Division agreed to accept the long-term (12 months) safety data for 100 subjects at the 120-day safety update.

2.6 Other Relevant Background Information

At the time of NDA submission, the sponsor requested a priority review for this product. That request was denied by the Division of Anesthetics, Critical Care and Addiction Drug Products with the following rationale:

> MaPP 6020.3 provides for priority review of new drugs that "if approved, would be a *significant improvement compared to marketed products*...in the treatment, diagnosis or prevention of a disease (*emphasis added*)... " The improvement may be manifest as the "elimination or a substantial reduction of a *treatment limiting* drug reaction... (*emphasis added*)"
>
> Ramelteon, a selective MT_1 and MT_2 receptor agonist, neither prevents insomnia nor affects the diagnosis of insomnia. The only possible reason for priority consideration would be demonstration of improved insomnia treatment. The sponsor proposed that ramelteon be granted a priority review due to the potential for "elimination or reduction of a treatment limiting drug reaction." The two major factors for their proposal are 1) the

medical and economic consequences of insomnia in the US that establish it as a public health burden and 2) the unmet need for safe effective treatment of insomnia without the deleterious side effects of the benzodiazepines, other benzodiazepine receptor agonists (BZRAs) and sedating antidepressants.

Insomnia may be an undertreated and underdiagnosed condition, however, the mere fact that a condition contributes to the public health burden does not require that drugs purporting to treat that condition should all receive priority review. In order to receive a priority review, a product should represent a *significant improvement compared to marketed products*. The sponsor claims that ramelteon has no potential for abuse, does not cause dependence, is not associated with withdrawal effects, does not cause rebound insomnia, and does not exhibit residual pharmacologic effects (p.4/22 of the provided rationale).

The potential for abuse and the issue of physical dependence do not represent *treatment limiting* drug reactions (*emphasis added*).

The limited rebound insomnia reported with the BZRAs does not represent a *treatment limiting* drug reaction (*emphasis added*).

The transient decrement in alertness seen after use of hypnotics, "so-called traveler's amnesia" does not represent a *treatment limiting* drug reaction but rather speaks to the need for use of good clinical judgment and the importance of patient education in prescribing (*emphasis added*).

While there may be treatment limiting drug reactions to the benzodiazepines in the elderly, the sponsor has not provided adequate data to support that these types of drug reactions exist with use of the BZRA in this population.

While review of the submitted data may reveal that ramelteon, with its novel mechanism of action, represents a beneficial addition to the available armamentarium of hypnotics, the rationale provided does not support the sponsor's claim that ramelteon provides a substantial improvement as compared to currently approved marketed products, specifically zaleplon and zolpidem.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review is being performed by Dr. Pramoda Maturu. The following comments are based upon his preliminary conclusions. The interested reader is referred to his final review for a detailed review of the CMC of this product.

Drug substance

- Highly pure ramelteon was used for the preclinical and clinical studies but a less pure substance is proposed for marketing. The [ ] impurity was increased from [ ] %.

Drug product

- The current acceptance specifications for ramelteon tablet dissolution needs to be set at a Q of — at 15 minutes for stability.
- The expiration date has to be revised based upon the dissolution specification of a Q of — at 15 minutes

Dr. Joan Buenconsejo of the Office of Biostatistics has performed a statistical analysis of the stability data. She found that the data, based upon a dissolution specification of — % at 15 minutes, support an expiration period of — months. However, if we were to accept use of a dissolution specification of — % at 15 minutes, the expiration period would be [ ]

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology review is being performed by Dr. Adam Wasserman. The following comments are based upon his preliminary conclusions. The interested reader is referred to his final review for a detailed review of the pharmacology/toxicology profile of this product.

Dr. Wasserman noted that 4-week administration of TAK-375 to both mice and rats significantly increased circulating melatonin levels at 1 hour and 12-14 hours (mice) and 1 hour and 15 hours after administration (rats). Return to baseline melatonin levels after cessation of drug administration was not determined in these rodent models. When given to animals, ramelteon, at high doses, lowers plasma testosterone and increases plasma luteinizing hormone.

At doses of 600 mg/kg or more, decreased locomotor activity, ataxic gait and hypothermia were seen in preclinical models. In rats the lethal dose ranged from 600 mg/kg (females) to 2000 mg/kg (males and some females).

Teratology studies showed abnormalities in the rat model though not in the rabbit: rats (600 mg/kg/day) showed small increases in the incidence of genital cysts, diaphragmatic hernia and skeletal variations; rabbits (at maternal toxic dose of 300 mg/kg/day) showed no developmental toxicity.

A study of postnatal effects in the rat demonstrated decreased viability, decreased body weight and delayed development at doses of 300/mg/kg/day without drug related effects being carried through to the F2 generation. Ramelteon was secreted into the milk of lactating rats. The no observed adverse effect level (NOAEL) was determined to be 30 mg/kg/day for general toxicity to dams/offspring. The NOAEL for female rat reproductive function was determined to be 100 mg/kg/day.

This product is noted to produce tumors of the Hardarian gland in mice and Leydig cell tumors in the rat. Hepatocellular adenomas and carcinomas are seen in both animal models. According to the sponsor, the increase in liver cell neoplasms seen in the rodent models was dose related. The sponsor postulated that this was due to induction of hepatic drug-metabolizing enzymes. The increase in Leydig cell tumors seen in rats given 1000 mg/kg/day was believed, by the sponsor, to be the result of ramelteon induced hormonal changes through melatonin inhibition of GnRH, LHRH and/or testosterone secretion (protocol TL-032, amendment 2). A positive genotoxicity finding was detected in one of the chromosomal aberration assays. At this point the pharmacotoxicologists would recommend that this product be classified as a "genotoxic carcinogen" and would recommend a pregnancy category C rating.

Preclinical studies were done to evaluate the potential for abuse of ramelteon. Since this is a new molecular entity with a novel mechanism of action, there was no known product that would be expected to have identical characterisitics. The sponsor used opiates and benzodiazepines as the closest possible positive controls. After daily treatment for one month (rats) or one year (monkeys), no physical drug dependence or withdrawal signs were noted upon cessation of drug administration. No drug-reinforcing effects of ramelteon were demonstrated in trials performed with rats or monkeys, though reinforcing behavior was shown to the positive controls used, e.g. diazepam, triazolam, midazolam.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The only source of clinical data was the materials submitted by the applicant in support of this New Drug Application.

I performed a complete review of the following submissions; all of which may be found filed under NDA 21-782 in the FDA Electronic Document Room:

1. 21 September 2004
   - The original submission
2. 4 October 2004
   - Debarment certification statements
3. 20 January 2005
   - 120 day safety update of the IAS with accompanying SAS files
   - Copies of CRFs for persons who withdrew due to an adverse event since the original NDA submission
   - The second interim report for long term safety study TL-022: " A Phase III, open-label fixed-dose study to determine the safety of long-term administration of TAK-375 in subjects with chronic insomnia" along with accompanying SAS files
4. 4 February 2005:
   - Proposed tradename and draft labels
5. 22 February 2005
   - Sample packaging (I did not review the pharmtox data in this submission)
6. 23 March 2005
   - Sample packaging
7. 12 May 2005:
   - Submission of references from the PFP-001 clinical trial report
   - Clarification of discrepancy in narrative for subject 12815/201725

4.2 Table of Clinical Studies

Table 1: Clinical studies

Study No. **PI or No. of CTRs** **Country**	**Study Design** **Primary Objective** **Subject Type**	**Treatment/Doses** **Number of Subjects**
Chronic Insomnia Population Placebo-Controlled Studies		
01-01-TL-375-005 (TL005) (13 centers) United States	Double-blind, placebo-controlled, 5-period crossover, randomized Safety, efficacy (PSG), dose-response evaluation Subjects with chronic insomnia (18-65 yr, inclusive)	Ramelteon 8 mg: 104 Ramelteon 16 mg: 107 Ramelteon 32 mg:103 Placebo: 103
01-01-TL-375-017 (TL017) (17 centers) United States	Double-blind, placebo-controlled, 3-period crossover, randomized Safety and efficacy (PSG) evaluation Elderly subjects ≥65 yr with chronic insomnia	Ramelteon 4 mg: 100 Ramelteon 8 mg: 100 Placebo: 100
01-01-TL-375-020 (TL020) (79 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety and efficacy evaluation for chronic insomnia Adult subjects (18-64 yr, inclusive) with chronic insomnia	Ramelteon 8 mg: 277 Ramelteon 16 mg:284 Placebo: 287
01-01-TL-375-021 (TL021) (29 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety and efficacy (PSG) evaluation for chronic insomnia Adult subjects (18-64 yr, inclusive) with chronic insomnia	Ramelteon 8 mg: 139 Ramelteon 16 mg:135 Placebo: 131
01-01-TL-375-025 (TL025) (136 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety and efficacy evaluation for chronic insomnia Elderly subjects (≥65 yr) with chronic insomnia	Ramelteon 4 mg: 281 Ramelteon 8 mg: 274 Placebo: 274
Chronic Insomnia Population, Long-term, Open-Label Study (Ongoing)		
01-01-TL-375-022 (TL022) (123 centers) United States	Open-label, Long-term safety, particularly endocrine assessment Subjects with chronic insomnia	Ramelteon 8 mg: 248 (≥ 65 yr) Ramelteon 16 mg: 965 (18-64 yr)
Healthy Volunteer Population		
PNFP 001 (PNFP001) [redacted]	Double-blind, placebo-controlled, randomized, ascending-dose Pharmacokinetic, pharmacodynamic, safety (including endocrine), and tolerability Healthy adult subjects (35-65 yr, inclusive)	Ramelteon 4 mg: 8 Ramelteon 8 mg: 8 Ramelteon 16 mg: 8 Ramelteon 32 mg: 8 Ramelteon 64 mg: 8 Placebo: 20
PNFP 002 (PNFP002) (14 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety and efficacy (PSG) evaluation for transient insomnia Healthy adult subjects (35-60 yr, inclusive)	Ramelteon 16 mg:126 Ramelteon 64 mg:126 Placebo: 123
01-01-TL-375-003 (TL003) [redacted]	Step 1: Open-label (pharmacokinetics) Step 2: Double-blind, placebo-controlled, 2-period crossover, randomized (pharmacodynamics) Pharmacokinetic(age and gender effects), pharmacodynamic, safety, and tolerability Healthy subjects: elderly (≥60 yr) and adult (18-35 yr, inclusive)	Step 1 Ramelteon 16 mg: 48 Step 2 Ramelteon 16 mg :44 Placebo: 44

Table 1, continued

Healthy Volunteer Population		
01-01-TL-375-004 (TL004) United States	Open-label, 2-period, crossover, randomized Pharmacokinetic (food effects), safety, and tolerability Healthy adult subjects (18-35 yr, inclusive)	Ramelteon 16 mg: 23 (fed state) Ramelteon 16 mg: 23 (fasted state)
01-01-TL-375-006 (TL006) Drs. Zammit United States	Double-blind, placebo-controlled, 4-period crossover, randomized PSG, Safety, melatonin secretion Healthy adult subjects (18-45 yr, inclusive)	Ramelteon 4 mg: 17 Ramelteon 16 mg: 17 Placebo: 16 5 mg melatonin: 17
01-02-TL-375-023 (TL023) (15 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety and efficacy(PSG) evaluation for transient insomnia Healthy adult subjects (18-64 yr, inclusive)	Ramelteon 8 mg: 98 Ramelteon 16 mg: 94 Placebo: 97
01-01-TL-375-031 (TL031) (3 centers) United States	Double-blind, placebo-controlled, parallel-group, randomized Safety, particularly endocrine assessment Healthy men and pre-menopausal women (18-45 yr, inclusive)	Ramelteon 16 mg: 50 Placebo: 49
01-01-TL-375-040 (TL040) United States	Single-blind, placebo-controlled, 4-period crossover, randomized Safety, particularly QTc and other ECG assessments, and pharmacokinetic Healthy men and women (at least 18 yr)	Ramelteon 32 mg: 56 Ramelteon 64 mg: 55 Placebo: 55 400 mg Moxifloxacin: 54
01-01-TL-375-032 (TL032) (23 centers) United States	Double-blind, placebo-controlled, parallel group, randomized Long-term safety, particularly endocrine assessment Healthy men and premenopausal women (18-45 yr, inclusive) with chronic insomnia	Ramelteon 16 mg: 57 Placebo: 65
EC 002 (EC002) United Kingdom	Double-blind, placebo-controlled, randomized, ascending dose Pharmacokinetic, pharmacodynamic, safety (including endocrine assessment), and tolerability Healthy adult subjects (18-60 yr, inclusive)	Ramelteon 16 mg: 20 Ramelteon 64 mg: 20 Placebo: 4
EC 003 (EC003) United Kingdom	Open-label, 2-period crossover, randomized Absolute bioavailability Healthy men (18-40 yr, inclusive)	Ramelteon 16 mg oral: 18 Ramelteon 2 mg IV: 20
EC 004 (EC004) United Kingdom	Open-label study using [^{14}C]-TAK-375 Absorption, metabolism, excretion Healthy men (30-50 yr, inclusive)	Ramelteon 16 mg: 6
Drug Interaction Studies		
01-01-TL-375-007 (TL007) United States	Open-label, 2-periodcrossover, randomized Pharmacokinetic (drug-interaction effect of ketoconazole), safety, and tolerability (CYP3A4 pathway) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg: 27 Ramelteon 16 mg (Day 4) + Ketoconazole 200 mg BID Days1-4: 28
01-01-TL-375-008 (TL008) United States	Open-label, 2-periodcrossover,randomized Pharmacokinetic(drug-interaction effect of fluvoxamine), safety, and tolerability(CYP1A2 pathway) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg: 25 Ramelteon 16 mg (Day 4) + Fluvoxamine 100 mg BID Days 1-4: 28
01-01-TL-375-009 (TL009) United States	Open-label, 2-period crossover, randomized Pharmacokinetic (drug-interaction effect of fluconazole), safety, and tolerability (CYP2C9 pathway) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg: 27 Ramelteon 16 mg on Day 4 + Fluconazole 400 mg on Day 1, 200 mg Days 2-4: 25

Table 1, continued

Drug Interaction Studies		
01-01-TL-375-024 (TL024) 1 United States	Open-label Pharmacokinetic (drug-interaction effect of midazolam), safety, and tolerability (CYP3A4 pathway) Healthy adult subjects (18-55 yr, inclusive)	Midazolam 10 mg on Day 1 followed by Ramelteon 32 mg for 9 Days followed by Ramelteon 32 mg + Midazolam 10 mg on Day 10: 28
01-01-TL-375-026 (TL026) United States	Open-label, 3-period, crossover, randomized Pharmacokinetic (drug-interaction effect of dextromethorphan), safety, and tolerability (CYP2D6 pathway) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 32 mg: 36 Dextromethorphan 30 mg: 34 Ramelteon 32 mg + Dextromethorphan 30 mg: 35
01-01-TL-375-027 (TL027) United States	Open-label, 2-period crossover, randomized Pharmacokinetic (drug-interaction effect of theophylline), safety, and tolerability (CYP1A2 pathway) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 32 mg: 18 Theophylline ER300 mg: 18 Ramelteon 32 mg + Theophylline ER300 mg: 34
01-01-TL-375-028 (TL028) United States	Double-blind, 4-period crossover, randomized Pharmacokinetic (drug-interaction effect of ethanol),safety, and tolerability Healthy adult subjects (21-55 yr, inclusive)	Ramelteon 32 mg: 22 Ramelteon 32 mg + Ethanol 0.6 g/kg: 23 Ethanol 0.6 g/kg: 23 Placebo: 23
01-01-TL-375-033 (TL033) United States	Open-label Pharmacokinetic (drug-interaction effect of warfarin), Pharmacodynamics (PT, INR), safety, and tolerability (CYP1A2 and CYP2C9 pathways) Healthy adult subjects (18-45 yr, inclusive)	Warfarin titration (7 to 9 Days) followed by Ramelteon 16 mg + Warfarin: 24
01-01-TL-375-034 (TL034) United States	Open-label Pharmacokinetic (drug-interaction effect of fluoxetine), safety, and tolerability (CYP2D6 pathway, some effects on 2C9, 2C19, 3A4) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg, 1 dose followed by Fluoxetine 40 mg for 10 Days followed by Ramelteon 16 mg + Fluoxetine 40 mg : 28
01-01-TL-375-035 (TL035) United States	Open-label Pharmacokinetic (drug-interaction effect of rifampin),safety, and tolerability (CYP induction) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 32 mg, 1 dose followed by Rifampin 600 mg for 10 days followed by Ramelteon 32 mg + Rifampin 600 mg: 28
01-01-TL-375-036 (TL036) United States	Open-label, 3-period crossover, randomized Pharmacokinetic (drug-interaction effect of omeprazole), safety, and tolerability (CYP2C19 pathway and CYP1A2 induction) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg: 29 Omeprazole 40 mg: 29 Ramelteon 16 mg + Omeprazole 40 mg: 30
01-01-TL-375-037 (TL037) United States	Open-label, 2-period crossover, randomized Pharmacokinetic (drug-interaction effect of digoxin), safety, and tolerability (P-glycoprotein substrate) Healthy adult subjects (18-55 yr, inclusive)	Ramelteon 16 mg + Digoxin 0.75 mg on Day 1 and 0.2 mg Days 2-12: 21 Digoxin 0.75 mg on Day 1 and 0.2 mg Days 2-12: 23

Table 1, continued

Drug Interaction Studies		
01-03-TL-375-043 (TL043) Canada	Double-blind, placebo-controlled, 4-period crossover, randomized Evaluate potential pharmacodynamic interactions between ramelteon and ethanol Healthy adult subjects (19-55 yr, inclusive)	Ramelteon 32 mg: 28 Ramelteon 32 mg + placebo: 28 Ramelteon 32 mg + ethanol 0.6 g/kg/ 20 min: 28 Placebo + placebo: 28
Disease Interaction Studies		
01-01-TL-375-014 (TL014) United States	Double-blind, ascending dose, 8-period crossover, placebo-controlled, randomized sequence Dose-finding safety study for abuse liability study Subjects with history of substance abuse or dependence (18-60 yr, inclusive)	Ramelteon 16 mg:6 Ramelteon 32 mg:6 Ramelteon 64 mg:6 Ramelteon 96 mg:6 Ramelteon 128 mg:6 Placebo:6 --- Triazolam 0.25 mg:6 Triazolam 0.75 mg:6
01-01-TL-375- 015 (TL015) United States	Double-blind, placebo-controlled, 7- period crossover, randomized Abuse liability study Subjects with history of hypnotic or anxiolytic drug abuse or dependence (18-60 yr, inclusive)	Ramelteon 16 mg: 14 Ramelteon 80 mg: 14 Ramelteon 160 mg: 14 Placebo: 14 --- Triazolam 0.25:14 Triazolam 0.50:14 Triazolam 0.75:14
01-01-TL-375-029 (TL029) United States	Open-label Pharmacokinetics (after single and multiple dosing), safety, and tolerability in subjects with hepatic impairment Healthy adult subjects (18-79 yr, inclusive) and subjects with hepatic impairment	Ramelteon 16 mg: 24 (healthy subjects) Ramelteon 16 mg: 24 (subjects with hepatic impairment) mild (n=12), moderate (n=12)
01-01-TL-375-030 (TL030) United States	Open-label Pharmacokinetics (after single and multiple dosing), safety, and tolerability in subjects with renal function impairment Healthy adult subjects (18-79 yr, inclusive) and subjects with renal impairment	Ramelteon 16 mg: 21 (healthy subjects) Ramelteon 16 mg: 29 subjects with renal impairment— mild (n=8), moderate (n=5), severe (n=7), on hemodialysis (n=9)
01-01-TL-375-038 (TL038) (6 centers) United States	Double-blind, placebo-controlled, 2-period crossover, randomized Safety and tolerability, including PSG Subjects with COPD (21-70 yr, inclusive)	Ramelteon 16 mg: 26 Placebo: 26
01-01-TL-375-039 (TL039) (5 centers) United States	Double-blind, placebo-controlled, 2-period crossover, randomized Safety and tolerability, including PSG Subjects with obstructive sleep apnea (21-64 yr, inclusive)	Ramelteon 16 mg: 26 Placebo: 26

Table 1, continued

Japanese Studies		
CPH 001 (CPH001) Japan	Double-blind, placebo-controlled, parallel-group, randomized, ascending single dose Pharmacokinetics (also food effects), pharmacodynamics, safety (including endocrine), and tolerability Healthy adult men (20-35 yr, inclusive)	Ramelteon 0.3 mg: 8* Ramelteon 1 mg: 8^ Ramelteon 2 mg: 7*+1 Ramelteon 4 mg: 7^+1 Ramelteon 8 mg: 8# Ramelteon 16 mg: 8 Placebo: 16## *Same subjects (Steps 1 and 3) ^Same subjects (Steps 2 and 4) #Some subjects received 8 mg in both 2-period crossover periods (fed vs. fasted) Step 5 ##12 of the 16 subjects received both placebo twice (Steps 1-5); the remaining 4 subjects received placebo once (Step 6)
CPH 002 (CPH002) Japan	Double-blind, placebo-controlled, parallel-group, randomized Pharmacokinetics, pharmacodynamics, safety (including endocrine), and tolerability Healthy adult men (20-35 yr, inclusive)	Ramelteon 8 mg: 8 Ramelteon 16 mg: 8 Placebo: 8
CPH 003 (CPH003) Japan	Double-blind, placebo-controlled, 3-period crossover, randomized Efficacy (PSG), safety (including endocrine) Healthy adult men (45-64 yr, inclusive)	Ramelteon 8 mg: 12 Ramelteon 32 mg: 11 Placebo: 11
CPH 005 (CPH005) Japan	Open-label Pharmacokinetic (age effects), safety (including endocrine), and tolerability Healthy elderly subjects (≥ 65 yr) and adult subjects (20-35 yr, inclusive)	Ramelteon 16 mg: 24
CPH 006 (CPH006) Japan	Double-blind, placebo-controlled, parallel-group, randomized Step 1: single-dose (early AM fast) Step 2: multiple-dose Pharmacokinetics, pharmacodynamics, safety (including endocrine), and tolerability Healthy adult men	Step 1 Ramelteon 32 mg: 8 Placebo: 4 Step 2 Ramelteon 32 mg: 8 Placebo: 4
CCT 001 (CCT001) (18 centers) Japan	Double-blind, placebo-controlled, 5-period crossover, randomized Safety and efficacy evaluation (PSG) for chronic insomnia Healthy adult subjects (20-64 yr, inclusive)	Ramelteon 4 mg: 62 Ramelteon 8 mg: 61 Ramelteon 16 mg: 63 Ramelteon 32 mg: 63 Placebo: 61

This is a modification of the list of studies presented in Appendix A of the IAS

4.3 Review Strategy

The sponsor's submission was emphasized in this review, with particular emphasis paid to the efficacy trials done in chronic insomnia. All trials were included in the safety analysis. I also used reference materials, as listed in section 11 of this review.

I, Dr. D. Elizabeth McNeil, was responsible for the synthesis and documentation of the overall conclusions of this application.

A review of the clinical endocrine data was provided by Dr. Mary Parks, of the Division of Metabolic and Endocrine Drug Products.

Dr. Dionne Price, of the Office of Biostatistics, performed the formal biometrics analyses of the efficacy data.

Dr. Pramoda Maturu, of the Office of New Drug Chemistry, performed the CMC review.

Dr. David Lee, of the Office of Clinical Pharmacology and Biopharmaceutics, reviewed the pharmacokinetics, pharmacodynamics and exposure-response data.

Dr. Adam Wasserman of the Pharmacology and Toxicology staff reviewed the pharmacology/toxicology data.

Dr. Katherine Bonson, of the Controlled Substances Staff (CSS), reviewed the abuse liability studies performed for this product.

4.4 Data Quality and Integrity

DSI was asked to audit the following sites, all of which contributed patients at a relatively high rate to the studies listed:

Name	Location	Protocol	# of patients enrolled
Gary Zammit	New York, NY	23/21	27/25
Renata Shafor	San Diego, CA	23/17/21	27/16/20
David Seiden	Pembroke Pines, FL	23/17/21/25	27/11/39/16
Curtis Kauffmann	Johnson City, TN	25	28

Dr. Zammit was investigated between 3 and 9 February 2005. The DSI investigator found the following violations of 21 CFR 312.62 [b], which requires that investigators maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

- Subject 211246 (Study TL021) has four different heights (61.5 inches, 69 inches, 71.5 inches, 72 inches) entered in the records, some of which would have rendered the subject ineligible for study due to the effect on the Body Mass Index calculation.

- The Body Mass Index was incorrectly calculated for subject 231265 (Study TL023) but the corrected value would not have affected study eligibility.

Dr. Shafor was investigated between 22 February and 15 March 2005. The DSI investigator found the following violations of 21 CFR 312.62 [b]:

- Potentially inaccurate case histories because the clocks at the study site and on the ECG machine were not set to the same time

- Protocol deviations in which patients did not complete the required testing 90 minutes (1.5 hours) prior to habitual bedtime while in the sleep laboratories, but rather within a range from 15 to 149 minutes prior to lights-out

Dr. Seiden was investigated between 15 March and 15 April 2005. Based on a preliminary evaluation of the EIR, the DSI investigator found the following violations of 21 CFR 312.62 [b]:

- Protocol and record keeping deficiencies, e.g. patients signing the wrong version of the consent form, incorrect codes entered as reasons for screen failure, crossed-out data that was not dated or initialed

- Incorrect positioning for PSG recordings for some subjects during TL-017 and TL-021

Dr. Kauffman was investigated between 28 February and 3 March 2005. The DSI investigator found the following violations of 21 CFR 312.62 [b], which requires that investigators maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

- There was a discrepancy between data recorded on source documentation and data reported on case report forms for subjects 252256 and 252470, both of whom had blank areas on the source document but completed areas on the corresponding areas of the CRFs.

- The study screening log indicated that subject 252030 was screened and given study drug on Day 1. The subject records do not indicate that any drug was given nor do the drug accountability records show that any drug was given.

- One of the 6 study blinding labels was missing in the study records for subject 252470

4.5 Compliance with Good Clinical Practices

All but one of the study sites appear to have been in compliance with good clinical practices. The sponsor reports that "site number 20759 [study TL-025] did not comply with critical procedures of the study (study report page 65 of 46629)." No further details of the non-compliance were given in the study report.

[*Reviewer's note: The sponsor was contacted, via email, on 24 May 2005, to ask for further information on the apparent non-compliance. On 1 June, Takeda informed us that site 20759 had apparent record-keeping deficiencies: "several subject diaries were considered potentially unreliable in that diaries did not always appear to be in the subject's handwriting and some diary data were apparently recorded by the study coordinator. [Takeda] also questioned whether the physical exams were always conducted by an appropriately licensed individual in that several pre-signed, blank exam reports were found on site. Takeda states that these findings were submitted to the IND for this application on 14 April 2004.*]

4.6 Financial Disclosures

Takeda exercised due diligence to ascertain the financial interests and arrangements of the principal and sub- investigators for studies 01-01-TL-375-005, PNFP002, 01-02-TL-375-017, 01-02-TL-020, 01-02-TL-375-021, 01-02-TL-375-023 and 01-02-TL-375-025. In study PNFP002, the financial disclosure information from sub-investigator [ ] was missing. Due diligence was performed by Takeda and documentation of those efforts was provided. The site, at which Dr. Vernon Pegram was the principal investigator, screened 8 patients, enrolling 6 patients.

Dr. [ ] (principal investigator) and [ ] (sub-investigator at Dr. [ ] site), submitted financial disclosure forms stating that they had received" significant payments of other sorts....from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria". These two investigators participated in studies [ ] and [ ] Dr. [ ] site enrolled no patients in study [ ] and enrolled [ ] [ ] in study [ ] Drs. [ ] are affiliated with [ ] consulting company, which received $1.4 million USD from Takeda "for consulting services exclusive of costs directly associated with study contact. (p.2 of provided financial disclosure information)" These payments were made after the filing of financial disclosure forms by Drs. [ ]

Reviewer's summary

The submitted financial information is adequate. Drs. [ ] site enrolled — of the participants on study [ ] They enrolled no patients on the other studies. [ ] is not one of the studies being used for the demonstration of efficacy. Dr. [ ] [ ]. The Agency's Division of Scientific Investigation was consulted on 4 April 2005 to contact Dr. [ ] and gain further insight into his role as consultant with [ ] :.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

[Reviewer's note: A pharmacokinetics review is being performed by Dr. David Lee of the Office of Clinical Pharmacology and Biopharmaceutics. The following comments are based upon his preliminary conclusions. The interested reader is referred to Dr. Lee's final review for detailed discussion of the pharmacokinetics data.]

Ramelteon has little affinity for the following types of receptors/receptor complexes: $GABA_A$. dopamine, serotonin, acetylcholine, glutamate, noradrenaline, opiate.

Ramelteon, the drug substance, is both highly soluble and highly permeable across the intestinal epithelia. While the oral absorption is 84%, the absolute bioavailability is 1.8% (range 0.5% to 12%) due to first-pass metabolism. The median T_{max}, after administration to healthy subjects, is 0.75 hours (range 0.5 to 1.5 hours). The product is primarily renally excreted as metabolites, with less than 0.1% of the dose excreted as parent compound.

All pharmacokinetic parameters for ramelteon show high intersubject variability. In fasted adults who received 16 mg of ramelteon, a 53-fold difference between minimum and maximum values and an 86-fold difference in AUC (0-∞) was seen.

The mean AUC and C max are dose proportional in humans at doses up to 64 mg, however the half life of ramelteon (1-2 hours) and the major metabolites M-I through M-IV (1 to 5 hours) is dose-independent. In two studies in which subjects received 7 days of dosing (16 or 64 mg in study EC002, 8, 16 or 32 mg QD in studies CPH 02, CPH 006), the ramelteon AUC was noted to be higher on Day 7 than on Day 1, though the M-II AUC was unchanged.

Ramelteon is converted to multiple metabolites, seven of which have been well characterized. M-II is the major metabolite in serum. The protein binding of ramelteon is 82% and of M-II is 77% in human serum. Most of the binding is on albumin.

The sponsor performed a food effect study, TL004, to assess the effect of fasting and of a high-fat, high-calorie meal on the absorption of ramelteon. The AUC (0-inf) was 31% higher and the C_{max} was 22% lower under fed conditions. The median T max was delayed by 45 minutes with food.

5.2 Pharmacodynamics

[Reviewer's note: A pharmacodynamics review is being performed by Dr. David Lee of the Office of Clinical Pharmacology and Biopharmaceutics. The following comments are based upon his preliminary conclusions. The interested reader is referred to Dr. Lee's final review for detailed discussion of the pharmacodynamics data.]

No pharmacodynamic effects were apparent during Phase I testing, except when ramelteon was given with alcohol.

5.3 Exposure-Response Relationships

[Reviewer's note: A review of the exposure-response relationships is being performed by Dr. David Lee of the Office of Clinical Pharmacology and Biopharmaceutics. The interested reader is referred to Dr. Lee's final review for detailed discussion of the data on exposure-response relationships.]

Based upon animal testing, the original dose proposed for human use was 16 mg. Multiples of 16 mg were used for most of the Phase I testing. During the development plan, it was found that 8 mg seemed to have comparable efficacy to the 16 mg dose so the lower dose is the one proposed for marketing.

Dr. Lee made the following recommendations for dose adjustments:
Table 2: Recommended dose adjustments

Factor	Ramelteon AUC	Ramelteon Cmax	M II AUC	M II Cmax	Sponsor's proposal	**Agency's proposal**
Gender Women	32 % ↑	19 % ↑	↔	↔	No adjustment	**No adjustment**
Renal* (Day 8)						
Mild	26 % ↓	36 % dec	33 % ↑			
Moderate	29 % ↑	65 % ↑	21 % ↓	22 % ↑	No adjustment	
Severe	81 % ↑c	21 % ↑	40 % ↑	↔No change		
Hemodialysis	50 % ↓	35 % ↓	29 % ↓	9 % ↓		
Food	31 % ↑	22 % ↓	↔	35 % ↓ Median Tmax prolonged 0.75 hr	30 minutes prior to bedtime;	**'Recommend not take with food,**
Elderly	97 % ↑	86 % ↑	30 % ↑	14% ↑	No adjustment	
Hepatic* (Day 8)						
Mild	258 % ↑	146 % ↑	29 % ↑	6 % ↓	No adjustment	
Moderate	967 % ↑	737 % ↑	↔	25 % ↓		
Severe	Not studied	Not studied	Not studied	Not studied		
1A2 inhibitor (fluvoxamine)	190-fold ↑	70-fold ↑	31 % ↑	60 % ↓		
3A4 inhibitor (ketoconazole)	84 % ↑	36 % ↑	93 % ↑	23 % ↑	No adjustment	**No adjustment**
2C9 inhibitor (fluconazole)	52 % ↑	44 % ↑	200 % ↑	55 % ↑		**Use with Caution**

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This product is proposed for the treatment of insomnia.

The sponsor has suggested the following wording, " [redacted]

]

6.1.1 Methods

[*Reviewer's note: The efficacy information in this section is limited to the primary endpoint, latency to persistent sleep, in support of the desired indication. I will be presenting the efficacy information for the recommended dose of 8 mg. In Appendix 10.2, I have presented the available efficacy information for all doses studied as part of the discussion of each clinical trial.*

Study PNFP-002 only utilized the 16 mg and 64 mg doses so the results will not be further discussed in this section. The interested reader is referred to Appendix 10.2 for further details of that study.

The interested reader is referred to the review by Dr. Dionne Price of the Office of Biostatistics for detailed discussion of the statistical analysis.]

6.1.1.1 PNFP002

The primary efficacy analysis for PNFP002 used the intent to treat (ITT) population which was defined as all subjects who were randomized and received at least one dose of study medication. This population was the primary one for analysis of safety, efficacy and residual pharmacological effects. The analyses were to be done on observed data collected at screening, day-1 check-in and day-2 check-out.

In the analysis of the primary efficacy variable, comparisons of each active treatment arm and placebo were to be made using Dunnett's t-tests and least squares means obtained from a two-way ANOVA with center, treatment and treatment by center interaction as factors. The mixed model procedure (PROC MIXED) with all effects fixed and Type III sums of squares were to be used to generate the ANOVA results.

Additional subgroup analyses defined by age ($\leq$50, >50), usual sleep time (<7.5 hour, $\geq$7.5 hours) and customary sleep latency (<20 minutes vs. > 20 minutes) were analyzed for latency to persistent sleep using a one-way ANOVA.

6.1.1.2 TL023

The intent-to-treat population (ITT) was to be defined as all subjects who were randomized and received one dose of study medication. This population was the primary one for analysis of safety, efficacy and residual pharmacological effects. The analyses were to be done on observed data collected at screening, day-1 check-in and day-2 check-out.

In the analysis of the primary efficacy variable, latency to persistent sleep, comparisons of each active treatment arm and placebo were to be made using Dunnett's t-tests and least squares means obtained from a two-way ANOVA with center and treatment as factors. The mixed model procedure (PROC MIXED) with all effects fixed and Type III sums of squares were to be used to generate the ANOVA results.

6.1.1.3 TL005

The intent-to-treat (ITT) population was defined as all subjects who were randomized and received at least one dose of double-blind study medication. The ITT population was to be analyzed for efficacy and safety.

Log transformation of the parameters would be applied for the primary efficacy variable, if the normality assumption for applying the ANOVA analysis was not met and the log-transformation was felt to be appropriate. If non-parametric approaches were used, the Kruskal-Wallis test was to be used to test the overall treatment of differences and the pairwise comparisons between each treatment arm and placebo.

Interactions such as treatment by age and gender would be investigated and formally evaluated only for the analysis of latency to persistent sleep. Those tests would be done at the 0.10 significance level.

6.1.1.4 TL017

The intent-to-treat (ITT) population was defined as all subjects who were randomized and received at least one dose of double-blind study medication. The ITT population was to be analyzed for efficacy and safety. Analysis for a given variable was only to include patients who had a value for that variable. If a patient were to receive an incorrect study medication, that subject would be removed from the analysis. The efficacy and safety analyses would be based upon the observed data.

The mean of the observations from the two nights of treatment would provide the data for analysis of the primary and secondary efficacy variables, residual pharmacological variables and special safety variables. All comparisons between the treatment groups were to be made using t-tests and least squares means and standard errors obtained from the following ANOVA model:

Parameter = seq+ subject (seq) + period +treatment + carryover

The treatment comparisons were to be made at the 0.05 significance level adjusted for two comparisons versus placebo using a stepwise testing procedure.

The efficacy of TAK-35 was to be assessed using Fisher's protected least significant difference (LSD) testing procedure to control the Type I error. The carryover effect was to be evaluated for the primary efficacy variable only. The carryover effect was to be removed from the analysis model for the primary efficacy variable if it was not found to be significant at the 0.100 level.

6.1.1.5 TL020

The sponsor analyzed the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of double-blind study medication. The efficacy analyses were to be based on a LOCF set, though analyses on observed data were presented as well.

Baseline values were defined as the average of non-missing observations from the single-blind placebo lead-in period. The protocol defined weekly time windows as nights 1-7, 8-14, 15-21, 22-28 and 29-last dose of double-blind study medication. The average of the non-missing data for a given weekly time window was to be analyzed when available. When data was unavailable for a given time window, the values from the last available time window were to be carried forward. During the study, the sponsor detected what were believed to be problems with data collection: "Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. For example, all data recorded on the CRF for Week 1 were analyzed for that visit. No recorded dates were checked." The SAP that was finalized for the study, prior to unblinding, included these changes.

The drug efficacy was assessed using Fisher's protected least significant differences (LSD) to control the Type I error, using Week 1 as the primary time point. Maintenance of efficacy was to be assessed at weeks 3 and 5 with a sequential testing procedure.

Comparisons between the treatment groups were made using t-tests with least squares means and standard errors derived from an ANCOVA model: parameter=baseline + center + treatment.

6.1.1.6 TL025

The intent-to-treat (ITT) population was the population to be used for analysis of efficacy and safety. While the ITT population was to consist of all randomized subjects who received at least one dose of double-blind study medication, in practice the analyses for a given variable would only include those patients who had a measurement for that variable.

The efficacy analysis was to be based on LOCF data, though the observed data would also be presented. ANOVA with treatment and pooled center as factors was to be used to evaluate baseline characteristics of the variables. Safety analyses were to be based upon observed data.

Comparisons between treatment groups were to be made using t-tests with least square means and standard errors obtained from the following ANCOVA model:

parameter=baseline+center+treatment

The mixed model procedure (PROC MIXED) with center and treatment effects fixed was to be applied. Type III sums of squares were to be used to generate the ANCOVA results. Since the primary efficacy analysis time point was week 1, the average of the available observations for Week 1 was to be analyzed. Maintenance of efficacy was to be assessed at week 3 and 5 using a sequential testing procedure.

Weekly time windows, i.e. nights 1-7, 8-14, 15-21, 22-28, 29-last dose of double-blind study medication, were defined for the collection of subjective assessment variables. The average of the available data for a weekly time window was to be analyzed. When no data was available for a time window, the values from the last available time window would be carried forward. The average of the available observations from the single-blind lead in period was to be considered the baseline. Observations from each day of the single-blind run-out period were to be used to assess rebound insomnia.

6.1.1.7 TL021

The intent-to-treat (ITT) population was the population to be used for analysis of efficacy and safety. While the ITT population was to consist of all randomized subjects who received at least one dose of double-blind study medication, in practice the analyses for a given variable would only include those patients who had a measurement for that variable.

The efficacy analysis, analysis of sleep architecture variables and the special safety variables from the post-sleep questionnaire were to be based on LOCF data, though the observed data would also be presented. ANOVA with treatment and pooled center as factors was to be used to evaluate baseline characteristics of the variables.

Comparisons between treatment groups was to be made using t-tests with least square means and standard errors obtained from the following ANCOVA model:

parameter=baseline+center+treatment

The mixed model procedure (PROC MIXED) with center and treatment effects fixed was to be applied. Type III sums of squares were to be used to generate the ANCOVA results. Since the primary efficacy analysis time point was week 1, the average of the available observations for Week 1 was to be analyzed. Maintenance of efficacy was to be assessed at week 3 and 5 using a sequential testing procedure.

The average of the available observations from the single-blind lead in period was to be considered the baseline. Weekly time windows, i.e. nights 1-7, 8-14, 15-21, 22-28, 29-last dose of double-blind study medication, were defined for the collection of subjective assessment variables. Any data collected in conjunction with the PSG assessments was to be analyzed according to the scheduled visit rather than the time window.

6.1.2 General Discussion of Endpoint

The primary efficacy parameter for the objective studies was latency to persistent sleep, defined as the elapsed time from the beginning of the PSG recording to the onset of the first 10 minutes of continuous sleep, i.e. the number of epochs from the beginning of the recording to the start of the first of 20 consecutive epochs of sleep divided by 2.

The primary efficacy parameter for the subjective studies was subjective sleep latency, i.e. the subject's perceived time to sleep onset.

[*Reviewer's note: The chosen primary endpoints are acceptable for use in support of a sleep onset claim. The definition of LPS is the standard one.*]

6.1.3 Study Design

Table 3: Designs used for efficacy studies

Study #	Design	Population
PNFP002	R, DB, PC, single dose	Healthy adults 35-60
TL023	R, DB, PC, single dose	Healthy adults 18-64
TL005	R, DB , PC, 5-period crossover, dose response, S/E	Healthy adults (18-65) w/ chronic insomnia
TL020	R, DB, PC, fixed dose S/E	Chronic insomniacs 18-64 yo
TL021	DB, PC, fixed dose, PSG + outpt S/E	Chronic insomniacs 18-64 yo
TL017	R, DB, PC, crossover, S/E	Chronic insomniacs >64 yo
TL025	R, DB, PC, fixed dose S/E	Chronic insomniacs > 64 yo

The chosen study designs effectively minimized bias through the use of blinding, randomization and crossover. The primary endpoints chosen to support a sleep onset claim were appropriate: latency to persistent sleep (LPS) in the objective PSG studies, time to sleep onset in the subjective studies.

Two short single-dose studies were done to evaluate efficacy in a sleep model laboratory model for transient insomnia. The study duration for evaluation of transient insomnia was appropriate.

The entry criteria used for the chronic insomnia studies, which were of adequate duration, were appropriate. One may appropriately generalize the findings from those studies to a larger population.

It is to be noted that the sponsor did perform studies in select patient subpopulations with diseases such as chronic obstructive pulmonary disease (COPD) and sleep apnea which are known to be associated with chronic insomnia. The latter studies are not discussed here but rather they are discussed in section 7.4.2.4.

6.1.4 Efficacy Findings

6.1.4.1 General comments on demographics and entry criteria

These studies enrolled both healthy adults (transient insomnia studies) and persons with chronic insomnia (all other studies). The majority of the participants were White (77.5%), female (57.8%) and < 65 years old (74.2%).

The entry criteria for the transient insomnia studies (key criteria are listed below) were appropriate and would allow one to generalize to a wider population:

Inclusion

- Healthy adults between 35 and 60 years old, inclusive
- Usual total sleep time between 6.5 and 8.5 hours, inclusive and usual sleep latency of no more than 30 minutes
- Habitual bedtime between 8:30 PM and 12 AM
- Within 20% of ideal body weight

Exclusion

- Previous sleep laboratory experience
- Epworth sleepiness scale of >10
- Sleep schedule changes required by employment within 3 months preceding Day 1 check-in or jet lag within the past 7 days
- Participation in a weight-loss program or alteration of exercise program within 30 days preceding Day 1 check-in
- Physical or psychiatric disorder that may be associated with a sleep disturbance
- Evidence of a significant illness including neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease

The entry criteria for the chronic insomnia studies (key criteria are listed below) were also appropriate and with the possible exception of the last two criteria listed would allow one to generalize to a wider population:

Inclusion

- Healthy adults with chronic insomnia (sSL ≥30 minutes, sTST less than 6.5 hours/night and daytime complaints associated with disturbed sleep) for at least 3 months
- A mean latency to persistent sleep of ≥20 minutes on 2 consecutive PSG screening nights with no night less than 15 minutes as well as a mean of at least 60 minutes of wake time during the 480 minutes in bed across 2 nights with no night less than 45 minutes
- Habitual bedtime between 8:30 PM and 12 AM

Exclusion

- Previous participation in a study involving TAK-375
- Use of any other investigational drug within 30 days or 5 half-lives, whichever was longer, prior to Day 1 of single-blind study medication
- Sleep schedule changes required by employment within 3 months preceding Day 1 check-in or had flown across greater than 3 time zones within the past 7 days

- Participation in a weight-loss program or alteration of exercise routine within 30 days preceding Check-in on Day 1
- History of schizophrenia, bipolar disorder, seizures, sleep apnea, COPD and/or mental retardation or cognitive disorder or history of psychiatric disorder, including anxiety or depression, within the previous 12 months
- History of alcohol abuse, drug addiction or drug abuse within the past 12 months
- Clinically significant illness within 30 days preceding Day 1 of study
- Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease, unless controlled and stable with protocol-allowed medication 30 days prior to Day 1 of the single-blind study medication
- Use of a central nervous system-active medication within 3 weeks (or 5 drug half-lives whichever is longer) prior to Day 1 of single-blind study medication. These medications must not have been used to treat psychiatric disease.
- Intent to use any medication during the study that is known to affect sleep/wake function or could interfere with the evaluation of study medication

6.1.4.2 Transient insomnia studies

PNFP002
This study only used the 16 and 64 mg doses so it will not be discussed in this section. The interested reader may find further details in the appendix.

TL023
Analysis of the data from the ITT population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.015). When considered individually, the results from the 8 mg group were significant (p=0.004) while those from the 16 mg were not (p=0.065). Log transformation and nonparametric analyses were performed as confirmatory analyses. The former analysis confirmed the primary analysis; the latter did not.

An evaluation by gender revealed statistically significant differences from placebo for males at both doses but not for females. An evaluation for age revealed statistically significant differences from placebo for persons < 40 years taking the 8 mg dose but not those taking the 16 mg dose. An evaluation by ethnicity revealed statistically significant differences from placebo for Caucasians who received the 8 mg dose only.

Table 4: LPS-ITT population

	Placebo (n=97)	Tak-375 8 mg (n=98)	Tak-375 16 mg (n=93)
LPS (minutes)			
LS mean (SE) LSM difference from placebo (SE) (95% CI)	19.7 (1.87)	12.2 (1.88) -7.6 (2.62) (-12.7, -2.4)	14.8 (1.93) -4.9 (2.65) (-10.1, 0.3)

(study report table 11.a)

Table 5: LPS-ITT population divided by gender

	Placebo	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)			
Males LS mean (SE) LSM difference from placebo (SE)	n=40 25.8 (3.79)	n=43 12.6 (3.79) -13.2 (5.22)*	n=44 14.1 (3.74) -11.7 (5.16)*
Females LS mean (SE) LSM difference from placebo (SE)	n=57 15.2 (1.70)	n=55 12.0 (1.82) -3.2 (2.48)	n=49 14.3 (1.87) -0.9 (2.51)

(study report table 11.d, * indicates statistical significance)

Table 6: LPS-ITT population divided by age

	Placebo	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)			
Age <40 LS mean (SE) LSM difference from placebo (SE)	n=77 16.7 (1.52)	n=83 11.3 (1.50) -5.4 (2.09)*	n=84 13.8 (1.48) -2.9 (2.08)
Age ≥40 LS mean (SE) LSM difference from placebo (SE)	n=20 33.7 (8.21)	N=15 12.0 (9.75) -8.7 (3.54)	N=9 17.1 (2.41) -5.0 (3.43)

(study report table 11.d, * indicates statistical significance)

Table 7: LPS-ITT population divided by ethnicity

	Placebo	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)			
Caucasian LS mean (SE) LSM difference from placebo (SE)	n=64 20.8 (2.52)	n=60 12.1 (2.59) -8.7 (3.54)*	n=68 15.7 (2.41) -5.0 (3.43)
Hispanic LS mean (SE) LSM difference from placebo (SE)	n=21 21.5 (4.31)	N=22 19.6 (4.20) -1.9 (3.78)	N=19 17.0 (3.72) -4.5 (4.13)
Other LS mean (SE) LSM difference from placebo (SE)	n=12 22.5 (7.37)	n=16 6.3 (5.57) -16.2 (8.91)	N=6 9.3 (10.73) -13.1 (11.36)

(study report table 11.d, * indicates statistical significance)

6.1.4.3 Chronic insomnia studies (Sleep laboratory)

TL005

A statistically significant treatment effect for active drug was seen when active drug at both doses was compared to placebo (p=0.001).

Table 8: LPS-ITT population

	Placebo (PBO) (n=103)	**TAK-375 4 mg (n=103)**	**TAK-375 8 mg (n=103)**
LPS (minutes)			
Mean (SD) LS mean (LSM) LSM-PBO	38.1 (35.36) 37.7	24.5 (21.58) 24.0 -13.7	24.6 (21.67) 24.3 -13.4
p-values for comparison		<0.001	<0.001

(modification of study report table 11a)

TL017

A statistically significant treatment effect in favor of active drug was seen when active drug was compared to placebo (p<0.001). An evaluation by gender revealed statistically significant differences from placebo for females at both doses but not for males. An evaluation by ethnicity revealed statistically significant differences from placebo for Caucasians only.

Table 9: LPS (minutes)-ITT population

	Placebo (PBO) (n=100)	**TAK-375 4 mg (n=100)**	**TAK-375 8 mg (n=100)**
LS mean (SE) LSM-PBO (SE) 95% CI for difference	38.4 (2.49)	28.7 (2.49) -9.7 (2.64) (-14.9, -4.5)	30.8 (2.52) -7.6 (2.68) (-12.9, -2.3)
Pairwise p-values		<0.001	0.005

(study report table 11a)

Table 10: LPS-ITT population divided by gender

	Placebo	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)			
Males LS mean (SE) LSM difference from placebo (SE)	n=37 35.3 (4.77)	n=37 26.2 (4.75) -9.1 (3.86)	n=37 28.5 (4.83) -6.8 (4.03)
Females LS mean (SE) LSM difference from placebo (SE)	n=63 40.1 (3.00)	n=63 29.9 (3.00) -10.1 (3.50)*	n=63 31.1 (3.02) -8.8 (3.55)

(study report table 11.d, * indicates statistical significance)

Table 11: LPS-ITT population divided by ethnicity

	Placebo	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)			
Caucasian LS mean (SE) LSM difference from placebo (SE)	n=95 37.5 (2.57)	n=95 28.5 (2.57) -9.0 (2.69)*	n=95 30.4 (2.60) -7.1 (2.74)*
Non-Caucasian LS mean (SE) LSM difference from placebo (SE)	n=5 51.5 (8.71)	N=5 28.9 (8.64) -22.5 (12.65)	N=5 39.6 (8.71) -11.9 (12.80)

(study report table 11.d, * indicates statistical significance)

6.1.4.4 Chronic insomnia studies (Outpatient)

TL020

The primary endpoint was the subjective sleep latency (sSL) from week 1 of double blind treatment, as recorded in subject diaries. No statistically significant treatment effect for active drug was seen when an analysis using LOCF data was performed (p=0.602 overall, with a p-value of 0.888 for the 8 mg group and 0.349 for the 16 mg group). The sponsor evaluated the trial using observed data as opposed to imputing data using LOCF. There were no statistically significant differences apparent with that analysis. The sponsor performed confirmatory log-transformation and non-parametric analysis. The results of said analyses confirmed the original finding. The sponsor performed a categorical analysis of the data after separating the patients into those who had baseline sSL of ≤30 minutes versus those who had baseline sSL > 30 minutes. There were no statistically significant differences apparent with that analysis.

TL025

The primary endpoint for this study was average subjective sleep latency, per subject diary, from nights 1 through 7 of double-blind treatment. Analysis of the data from the ITT population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.009), as well as when considered individually: 4 mg group (p=0.008), 8 mg group (p=0.008).

Table 12: sSL-ITT population (LOCF data)

	Placebo (n=274)	Tak-375 4 mg (n=280)	Tak-375 8 mg (n=272)
sSL (minutes)			
LS mean (SE) LSM difference from placebo (SE) (95% CI)	78.5 (2.24)	70.2 (2.21) -8.3 (3.10) (-14.4, -2.2)	70.2 (2.24) -8.3 (3.12) (-14.5, -2.2)

(study report table 11.a)

Log transformation and nonparametric analyses were performed as confirmatory analyses. The former analysis confirmed the primary analysis; the latter did not, although the trend reflected

the primary analysis. The results from analysis of the per-protocol population were consistent with those from analysis of the ITT population.

The sponsor performed a categorical analysis using LOCF data from the ITT population after separating the patients into those who had baseline sSL of ≤30 minutes versus those who had baseline sSL > 30 minutes.

Table 13: sSL (minutes)-Responder analysis performed by sponsor

SSL	Placebo n, (%)	Ramelteon 4 mg n, (%)	Ramelteon 8mg n, (%)	Overall p-value
Baseline				
n	274	281	273	
≤30 min	9 (3.3)	8 (2.8)	5 (1.8)	
>30 min	265 (96.7)	273 (97.2)	268 (98.2)	
Week 1				0.716
n	274	280	273	
≤30 min	42 (15.3)	49 (17.5)	43 (15.8)	
>30 min	232 (84.7)	231 (82.5)	230 (84.2)	
p-value for comparison with placebo		0.353	0.731	
Week 3				0.042
n	274	280	273	
≤30 min	54 (19.7)	71 (25.4)	76 (27.8)	
>30 min	220 (80.3)	209 (74.6)	197 (72.2)	
p-value for comparison with placebo		0.072	0.010	
Week 5				0.474
n	274	280	273	
≤30 min	71 (25.9)	80 (28.6)	81 (29.7)	
>30 min	203 (74.1)	200 (71.4)	192 (70.3)	
p-value for comparison with placebo		0.349	0.225	
Placebo run-out				0.448
n	226	233	238	
≤30 min	59 (26.1)	64 (27.5)	69 (29.0)	
>30 min	167 (73.9)	169 (72.5)	169 (71.0)	
p-value for comparison with placebo		0.340	0.244	

(data from table 14.2.1.7 in the final study report for TL025)

[*Reviewer's note: One site for this study, TL025, was found to have record-keeping deficiencies. Although the final study report states that the patients from this site were excluded from analysis, in reality, according to an email sent from Steven Danielson, "some subjects from this site were included in the ITT analysis as well as in the PP analysis.*

Takeda is reanalyzing the PP population excluding the patients from the site in question to determine whether their exclusion will affect the study outcome. Takeda's preliminary conclusion, as of 1 June 2005 (the date of the email), is that the new analysis is consistent with the original. The final assessment is still pending. Our reassessment of the data, excluding the site in question, showed results that were consistent with the original finding.]

The analysis of results divided by gender revealed that the 4 mg dose produced statistically significant results in females at weeks 1 and 5 and the 8 mg dose produced statistically significant results in females at week 5 only.

Table 14: sSL-ITT population divided by gender

	Tak-375 4 mg	Tak-375 8 mg
LPS (minutes)		
Males Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=110 -7.3 (5.23) -0.9 (5.75)	n=122 -10.4 (5.09) -9.6 (5.60)
Females Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=170 -8.2 (4.26)* -10.6 (4.22)*	n=150 -8.2 (4.26) -12.9 (4.36)*

(tables 14.2.1.11.2-14.2.1.13.2 in final study report, * indicates statistical significance)

The sponsor performed an analysis divided by ethnicity. The results were significant in Caucasians at weeks 1 (4mg and 8 mg doses) and at week 5 (8 mg dose).

Table 15: sSL-ITT population divided by ethnicity

	Tak-375 4 mg	Tak-375 8 mg
LPS (minutes)		
Caucasian Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=251 -7.5 (3.30)* -6.4 (3.46)	n=239 -8.6 (3.35)* -12.4 (3.51)*
Females Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=29 -10.8 (10.53) -24.9 (13.02)	n=33 -7.8 (10.45) -29.1 (12.93)

(tables 14.2.1.11.2-14.2.1.13.2 in final study report, * indicates statistical significance)

6.1.4.5 Chronic insomnia studies (Sleep laboratory and outpatient)

TL021

A statistically significant overall treatment effect in favor of active drug, in the ITT population based upon LOCF data, was seen when active drug was compared to placebo at weeks 1 ($p<0.001$), 3 ($p<0.001$) and 5 ($p<0.003$). At weeks 1, 3, and 5 both studied doses were also superior to placebo when reviewed individually: 4 mg was statistically significant at levels of <0.001, 0.001 and 0.007 respectively; 8 mg was statistically significant at levels of <0.001,

<0.001 and 0.002 respectively. The analysis of the observed data was consistent with the results obtained from analysis of the LOCF data. The sponsor performed log transformation and nonparametric analyses to confirm the findings from the primary analysis. These confirmatory measures were in agreement with the findings from the primary analysis. When the PP population was evaluated, using LOCF data, only the ramelteon 16 mg group showed a statistically shorter LPS at weeks 1 and 3. The sponsor attributes this to the smaller sample size in the PP population.

Table 16: LPS (minutes)-ITT population

	Placebo (PBO) (n=131)	**Ramelteon 8 mg (n=139)**	**Ramelteon 16 mg (n=135)**
Baseline			
N	131	139	135
LS mean (SE)	65.3 (3.54)	64.3 (3.46)	68.4 (3.54)
Week 1			
N	131	138	135
LS mean (SE)	47.9 (2.72)	32.2 (2.67)	28.9 (2.71)
LSM-PBO (SE)		-15.7 (3.70)	-18.9 (3.73)
95% CI for difference		-22.9, -8.4	-26.3, -11.6
Week 3			
N	131	138	135
LS mean (SE)	45.5 (2.93)	32.6 (2.87)	27.9 (2.92)
LSM-PBO (SE)		-12.9 (3.98)	-17.6 (4.02)
95% CI for difference		-20.7, -5.1	-25.5, -9.7
Week 5			
N	118	124	135
LS mean (SE)	43.6 (3.39)	31.5 (2.91)	29.5 (2.96)
LSM-PBO (SE)		-11.0 (4.03)	-12.9 (4.07)
95% CI for difference		-18.9, -3.1	-20.9, -4.9

(study report table 11a)

The sponsor's analysis by gender revealed statistically significant results for both genders.

Table 17: LPS-ITT population divided by gender

	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)		
Males		
Week 1	n=57	n=46
LSM difference from placebo (SE)	-19.4 (7.94)*	-26.0 (8.18)*
Week 5		
LSM difference from placebo (SE)	-24.0 (10.00)*	-22.9 (10.29)*
Females	n=81	n=89
Week 1	-15.5 (4.45)*	16.6 (4.31)*
LSM difference from placebo (SE)		
Week 5	-8.8 (4.0)*	-10.8 (3.88)*
LSM difference from placebo (SE)		

(tables 14.2.1.11.2-14.2.1.13.2 in final study report, * indicates statistical significance)

The sponsor's analysis by age revealed statistically significant results for people who were under 40 years old.

Table 18: LPS-ITT population divided by age

	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)		
< 40 years Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=82 -21.5 (4.57)* -17.1 (5.14)*	n=69 28.1 (4.80)* -21.3 (5.40)*
≥ 40 years Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=56 -8.8 (6.26) -4.5 (6.65)	n=66 -8.0(5.97) -1.9 (6.35)

(tables 14.2.1.11.2-14.2.1.13.2 in final study report, * indicates statistical significance)

The sponsor's analysis by ethnicity revealed statistically significant results for Caucasians and Hispanics at 8 mg and for Caucasians, Blacks and Hispanics at 16 mg during Week 1. When evaluated at week 5, the results were only significant for Blacks at 16 mg.

Table 19: LPS-ITT population divided by ethnicity

	Tak-375 8 mg	Tak-375 16 mg
LPS (minutes)		
Caucasian Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=87 -13.6 (5.10) -9.5 (5.42)	n=82 -16.3 (5.20) -8.2 (5.52)
Black Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=19 -17.9 (10.47) -17.6 (12.71)	n=23 -25.0 (9.98)* -24.5 (12.10)*
Hispanic Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=26 21.1 (7.84)* -10.5 (8.49)	n=27 -29.0 (7.61) -12.9 (8.25)
Other Week 1 LSM difference from placebo (SE) Week 5 LSM difference from placebo (SE)	n=6 -36.0 (15.00) 33.9 (55.59)	n=3 -41.5 (16.26) 6.4 (60.25)

(tables 14.2.1.11.2-14.2.1.13.2 in final study report, * indicates statistical significance)

6.1.4.6 Summary tables

Table 20: Latency to persistent sleep in transient insomnia (PSG measurement)

		Ramelteon Dose			
Study	**Placebo**	**8 mg**	**16 mg**	**64 mg**	**Overall P-value**
PNFP002	(N=123) 22.6	--	(N=124) 12.2*	(N=123) 13.4*	<0.001
TL023	(N=97) 19.7	(N=98) 12.2*	(N=93) 14.8	--	0.015

This is the sponsor's table depicting least square means (LSM) in minutes, with *indicating statistical significance.
(table 4c from clinical overview section of the NDA)

Table 21: Latency to persistent sleep in chronic insomnia (PSG measurement)

Study Visit		Ramelteon Dose				Overall P-value
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**	
TL005	37.7	24.0*	24.3*	24.0*	22.9*	<0.001
TL017	38.4	28.7*	30.8*	--	--	<0.001
TL021						
Baseline	65.3	--	64.3	68.4	--	--
Week 1	47.9	--	32.2*	28.9*	--	<0.001
Week 3	45.5	--	32.6*	27.9*	--	<0.001
Week 5	42.5	--	31.5*	29.5*	--	0.003

This is a modification of the sponsor's table depicting least square means (LSM) in minutes, with *indicating statistical significance.
(table 4d from clinical overview section of the NDA)

Table 22: subjective sleep latency in chronic insomnia

Study Visit		Ramelteon Dose				Overall P-value
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**	
TL005	57.0	50.9	46.7	43.9*	46.5	0.040
TL017	58.2	48.2*	50.9	--	---	0.096
TL021						
Baseline	74.7	--	71.4	77.8	--	--
Week 1	64.3	--	62.9	59.7	--	0.351
Week 3	61.8	--	56.6	53.4*	--	0.033
Week 5	57.1	--	52.5	53.5	--	0.325
TL020						
Baseline	85.5	--	85.2	92.5	--	--
Week 1	74.4	--	74.8	77.2	--	0.602
Week 3	70.7	--	69.5	69.3	--	0.872
Week 5	66.5	--	64.1	65.2	--	0.737
TL025						
Baseline	84.2	83.5	86.6	--	--	
Week 1	78.5	70.2*	70.2*	--	--	0.009
Week 3	69.3	64.9	60.3*	--	--	0.013
Week 5	70.6	63.4*	57.7*	--	--	<0.001

This is a modification of the sponsor's table depicting least square means (LSM) in minutes, with *indicating statistical significance.
(table 4f from clinical overview section of the NDA)

6.1.5 Clinical Microbiology

This section is not applicable to this NDA submission.

6.1.6 Efficacy Conclusions

6.1.6.1 Statistician's comments

Ramelteon appears to promote sleep latency, on objective measures, during the first week of treatment. The sponsor has not demonstrated that this effect is maintained over time.

Immediate effect (Week 1 data)

- Study 017, performed in an elderly population, demonstrated efficacy of the 8 mg dose based on the mean latency to persistent sleep (LPS).
- Study 021, performed in non-elderly adults, demonstrated efficacy of the 8 mg dose based on the mean latency to persistent sleep (LPS).
- Study 020, performed in non-elderly adults, did not demonstrate efficacy of the 8 mg dose based on the subjective assessment of time to sleep onset.
- Study 025, performed in an elderly population, demonstrated efficacy of the 8 mg dose based on the subjective assessment of time to sleep onset in the analysis of means but not in the responder or the categorical analyses. Dr. Price examined the cumulative distribution fractions of each treatment arm and found little difference in the proportion of values less than 30 minutes, though reductions from large values to less large values were noted, accounting for the overall reduction in mean latency.

Maintenance of effect (35 day studies)

- Study 020, performed in non-elderly adults, did not demonstrate efficacy of the 8 mg dose based on the subjective assessment of time to sleep onset.
- Study 21 demonstrated maintenance of effect according to the sponsor's LOCF analysis. In the BOCF analysis performed by Dr. Price, effect did appear to be maintained past week 1. The responder analysis performed by Dr. Price did not demonstrate maintenance of drug effect.
- Study 25 demonstrated maintenance of effect according to the sponsor's LOCF analysis. In the BOCF analysis performed by Dr. Price, effect appeared to be maintained past week 1. Neither the responder analysis performed by Dr. Price nor the responder analysis performed by the sponsor demonstrated maintenance of drug effect.

6.1.6.2 Clinical reviewer's comments

The sponsor's primary goal was to demonstrate that ramelteon decreased sleep latency when measured by objective measures, i.e. polysomnography, or measured by subjective measures, i.e. sleep diaries/questionnaires.

While study TL023 did not replicate the finding of efficacy for the 16 mg dose found in PNF002, it did objectively demonstrate, using a sleep laboratory model of transient insomnia, that a single 8 milligram dose would decrease sleep latency in healthy adults.

In all of the chronic insomnia studies which used objective measures of sleep latency, ramelteon was demonstrated to decrease sleep latency at all doses studied for the first 7 days of treatment. In one of the studies, TL025, which used subjective measures to evaluate time to sleep onset, the sponsor found using an analysis of means, an immediate and a persistent effect of ramelteon. Neither the sponsor's responder analysis nor the responder analysis done by Dr. Price supported this finding.

The effect of ramelteon was maintained through the 35-day study period as determined by the analysis of means performed by the sponsor on studies 021, which used objective measures as the primary means of evaluation, and 025, which used subjective measures as the primary means of evaluation. In Dr. Price's responder analyses of these same studies, the effect of ramelteon was not maintained over the 35-day period. The sponsor's responder analysis also failed to demonstrate that an effect was maintained over the 35 day period.

While the sponsor was able to provide objective evidence of an immediate effect on sleep latency, there is a paucity of the expected subjective support. Even in trials where there was clear evidence of a decrease in sleep latency, the subjective determinations of total sleep time and sleep quality did not mirror the objective findings. The results from the one positive subjective study depend upon the method of analysis used although in fairness it should be stated that the sponsor used the pre-specified method of analysis and the findings were positive using that analysis method.

The results from sub-group analyses by gender, age, or ethnicity were inconsistent across studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

[Reviewer's note: Unlike in the efficacy section where I primarily restricted the discussion to the recommended dose of 8 mg, in this section I will be discussing the adverse events seen at all doses studied.

The sponsor made a determination of treatment-emergent adverse events and only included those in the IAS listings. In those instances where I disagreed with their determination, I have noted the disagreement and added the adverse event to the adverse events table included later in this review.

The data used for this section consists of the sponsor's narrative summaries, line listings and case report forms. The sponsor considered the last evening that the subject took a dose of study drug to be post-dosing Day 1, i.e. if a patient were to take study drug on Monday, then Tuesday would be post-dosing Day 2, not Day 1 as would have seemed intuitive.]

7.1.1 Deaths

At the time of the initial submission, the sponsor reported the deaths of two participants, both of whom were receiving 16 mg of ramelteon in study TL022. There were no additional deaths reported at the time of the 120 day safety update.
[Reviewer's note: I reviewed the CRFs for both of these patients.]

Subject: 12646/221471[ ]
This 57 year old woman, died on Study Day 159, after having been struck by a motor vehicle while she was walking down a highway at 2:30 AM.

Toxicology studies were only positive for ethanol: vitreous ethanol 0.270 gm/dl, blood ethanol 0.238 gm/dl, urine ethanol 0.284 gm/dl. Her autopsy findings, which included but were not limited to a tear in the thoracic aorta, mediastinal hemorrhage, subgaleal hemorrhage and subarachnoid hemorrhage, were consistent with having been struck by a moving motor vehicle.

She had initiated treatment on 10 September 2003 as per p.13 of her CRF. She was last seen on December 31 2003, in treatment period month 4, as per page 22 of her CRF. On page 37 of her CRF, it says that the date of her last study dose was 02 January 2004 and she died on [ ]. It is unclear how it was determined that the last dose was 02 January 2004.

While there is not a clear causal connection, it is not possible to completely rule out an association with study drug, since the sponsor has demonstrated that the combination of ramelteon and ethanol may produce psychodynamic effects.

[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety because, according to the CRF, the last dose of study drug was 2 January 2004 and her date of death was* [ ] *later. I am unclear how it was determined that the last dose of study drug was 02 January 2004. If no data can be shown to demonstrate that she could not have been using ramelteon concurrent with ethanol on the date of her demise, I would consider this treatment-emergent. The sponsor was been sent an e-mail (1 June 2005) to ascertain how they determined the last day of study dosing. The sponsor responded that the last diary entry completed was from 2 January 2004 therefore that was felt to be the last documented day of study drug dosing. I can appreciate that rationale and will accept it.*]

Subject: 12654/211056/[ ]
This 58 year old man, who had been a previous participant in TL021, was on Study Day 227 when he was struck by a motor vehicle while crossing a parking lot. He had taken his last dose of study medication the night before, Study Day 226. His death on study Day 229 was attributed to blunt head trauma. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

7.1.2 Other Serious Adverse Events

[*Reviewer's note: I have elected to divide the subjects with serious adverse events into two groups.*

In section 7.1.2.1, I provide the narratives for all of the patients who had serious adverse events which led to discontinuation. I reviewed the CRFs for all of the patients who had serious adverse events which led to discontinuation.

In section 7.1.2.2, I provide the narratives for all of the patients who had serious adverse events which did not lead to discontinuation.]

7.1.2.1 Serious adverse events which led to discontinuation

Subject 12815/201725 [TL 020]
SAE: Convulsions NOS, diabetes mellitus non-insulin dependent
This 55 year old woman, with a past medical history significant for hypertension, migraine headaches, and acquired hypothyroidism, was receiving ramelteon 16 mg. Her concomitant medications included BC powder (aspirin/caffeine/salicylamide), levothyroxine, conjugated estrogens and ibuprofen. She had taken a dose of study medication on Day 38. On Day 39, she presented to a local emergency room for treatment of headache, nausea and seizure. She was hospitalized for further evaluation. Brain imaging, including CT, MRI and angiogram, did not reveal any abnormalities; all studies were done without contrast. Her glucose level was 218 mg/dL; she was given a no-caffeine American Diabetic Association diet along with diabetic teaching. The sponsor states that "drug screens for benzodiazepines and tricyclics were positive and antidepressants were negative." While hospitalized, she was treated with valproic acid, quetiapine, rofecoxib, pantoprazole, fluoxetine, pioglitazone, metformin, magnesium, potassium, and nalbuphine.

The provided narrative states that she was discharged on Day 36 in fair condition with discharge diagnoses of seizure disorder, migraine headaches, diffuse body aches, possible withdrawal from outpatient narcotics and positive postictal phenomenon. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.
[*Reviewer's note: This narrative contains inconsistencies. The provided narrative states that she was discharged on Day 36 but earlier her admission day is given as Day 39. The narrative states that hypomagnesemia was part of her presenting list of symptoms but no magnesium level was provided. The basis for the diagnosis of diabetes is not clear, and it is noted that this diagnosis was not one of the ones stated at discharge. Her discharge diagnosis includes possible withdrawal from outpatient narcotics, but the toxicology screen was not positive for opiates nor were opiates among her list of concomitant medications.*

The study termination page in her CRF (p.38) states that she discontinued due to an adverse event. The adverse events listed include migraine headache on [ ] worsening severity of illness (insomnia) [ ], nausea and seizure from [ ]. The data clarification form (p. 38/147) stated that she was discontinued due to use of seroquel from 7 July -8 July 2003.

Takeda was sent an email on May 9 requesting clarification of the apparent discrepancies. The following information was provided: Patient received her first dose of placebo lead-in medication on [ ] and her first dose of ramelteon 16 mg on [ ]. She was hospitalized on Day 39, one day after she stopped study medication. The diagnosis of Type II diabetes was made, by the PI, based on the glucose level of 216 at the time of hospital admission. Her follow up glucose, taken the next day, was 90 mg/dl. Diabetes is not mentioned in her hospital discharge summary though it is listed on her CRF. The issue of potential withdrawal form outpatient opiates has not been resolved.

In my opinion, the listing of diabetes mellitus as an SAE for this patient is in error. I have omitted it from the listing of adverse events.]

Subject 12591/222030 [TL 022]
SAE: deep venous thrombosis
A 72 year old woman who had been receiving 8 mg of ramelteon daily was hospitalized on Study Day 14 due to a deep vein thrombosis in her right leg. Her past medical history was significant for bilateral hip replacement with a subsequent revision. By patient report, she had had three months of right leg swelling. A Doppler ultrasound revealed a deep venous thrombosis extending from her distal right superficial femoral vein to the right popliteal vein. She was treated with Lovenox and warfarin. The event resolved on Study Day 20. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12074/170154 [TL022]
SAE: Colon cancer NOS
A 72 year old man, who had recently completed study TL017, received ramelteon 8 mg while participating in study TL022. His last dose of study drug was on 13 Jan 2004. On [ ] he was hospitalized for evaluation and treatment of study drug. The patient was withdrawn from

the study upon admission to the hospital. The colon cancer was probably not related to study drug use.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety since, according to their definition, the event occurs 8 days post-study dose. I disagree but will consider it a late effect so that the sponsor's definition will be applied consistently.*]

Subject 12651/222003[TL 022]
SAE: cerebrovascular accident (cerebellar)
A 72 year old man, who had been receiving 8 mg ramelteon daily, had new onset unsteadiness, nausea and blurry vision lasting 30 minutes on Study Day 318. On Day 319, he had a recurrence of the same symptoms. His use of study drug was discontinued that day. On Day 320, he was hospitalized for evaluation of a cerebellar cerebrovascular accident. An MRI revealed small vessel ischemic changes, old lacunar infarcts of the basal ganglia and small acute infarcts in the right cerebellum and at the cerebellar vermis. His medical history was significant for hypertension, left carotid bruit, and average daily alcohol intake of 2 cocktails. His concomitant medications included ibuprofen, fosinopril and aspirin. He was treated with coumadin during his hospitalization and was discharged on Day 327. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12657/25117[TL 022]
SAE: cholelithiasis, benign prostatic hyperplasia
A 74m year old man, who had previously completed study TL025, was randomized to ramelteon 8 mg. He received his last dose of study drug on Day 71. The next day, he was hospitalized for a cholecystectomy following 20 hours of severe right upper quadrant pain. Postoperatively, he underwent two endoscopic retrograde cholangiopancreatographies and ultimately a small jagged common bile duct stone was removed. He was discharged on Day 76 with a foley catheter in place as he was having difficulty with micturition. On Day 91, he was hospitalized for treatment of worsening prostatic hypertrophy and underwent a transurethral resection of the prostate. He was discharged on Day 95. He was discontinued from the study on Day 104. These adverse events were probably not related to the use of study drug.
[*Reviewer's note: The sponsor considered only the cholelithiasis treatment emergent for the integrated analysis of safety. I agree. The worsening of the benign prostatic hyperplasia occurred twenty days after his last dose of study drug. I did not add the latter event to the listing of treatment emergent adverse events.*]

Subject 12676/211021[TL 022]
SAE: Ectopic pregnancy
A 21 year old woman, who had completed study TL021, was receiving ramelteon 16 mg. She was found to have a positive pregnancy test on Study Day 28, at which time she was withdrawn from the study. Her last day of study drug use was Day 27. On Day 32, the pregnancy was confirmed with a serum pregnancy test. On Day 41, she was diagnosed with an ectopic pregnancy. On that same day, the patient underwent a laparoscopic salpingectomy. This adverse event was probably not related to use of study drug.

[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. Fertilization and implantation of the zygote both occurred while the patient was still enrolled on the study, insofar as may be determined. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 12676/222031[TL 022]

SAE: Pneumonia with associated empyema

A 65 year old man was receiving ramelteon 8 mg when, on Day 26, he was hospitalized for treatment of a right lung pneumonia with associated empyema. His initial illness started one month prior to hospitalization with hemoptysis associated with production of dark sputum. He was also noted to have fever, night sweats and pleuritic chest pain. On Day 29, he underwent a right thoracotomy with decortication and wedge excision of a right lower lobe abcess. He improved postoperatively and was discharged from the hospital on Day 34. He was discontinued from the study due to this hospitalization. This adverse event was probably not related to the use of study drug.

Subject 12700/211084[TL 022]

SAE: chest discomfort, chest pain

AE: coronary artery occlusion, carotid artery stenosis, chest pain post triple bypass surgery

A 59 year old woman, who had previously completed study TL021, was hospitalized on Day 67 for chest discomfort including severe left sided chest pain and pressure radiating down her left arm associated with mild nausea. The cardiologist who evaluated her diagnosed acute coronary syndrome in association with high-risk features and recommended coronary artery bypass surgery. Her past medical history was notable for coronary artery disease, type II diabetes, acute myocardial infarction of the inferior wall, angina, hypertension, peripheral vascular disease, cerebrovascular accident, stent placement to the left posterior descending artery, left carotid endarterectomy surgery and dyslipidemia. She was withdrawn from the study on Day 79. She was rehospitalized on Day 114. On Day 119, she was discovered to have amaurosis fugax in association with carotid artery stenosis. On that same day, she underwent a right carotid endarterectomy as well as 3-vessel bypass surgery for treatment of her 5 blocked arteries. On Day 130, she was hospitalized with chest pain that resolved after treatment with nitroglycerin and morphine. She was discharged on Day 132. She was seen in the emergency room on Day 139 and hospitalized for chest pain. She was discharged on Day 141 with her angina attributed to distal disease as opposed to a blockage of the recent bypass grafts. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.
[*Reviewer's note: The sponsor considered only the chest discomfort and chest pain treatment emergent for the integrated analysis of safety. I agree as the other AE appear to be re-statements of the SAE. I did not add the other events to the listing of treatment emergent adverse events.*]

Subject 12701/221049 [TL 022]

SAE: angina unstable

A 58 year old man, with a past medical history significant for hypertension and tobacco use, was discontinued from the study having received his last dose of ramelteon 16 mg on Day 12. On Day 27, he was hospitalized for evaluation and treatment of unstable angina. He had been complaining of recurring "grabbing tightness in the middle of his chest" and occasional jaw

discomfort for 10-14 days prior to hospital admission. A catheterization revealed a 99% occlusion of the right coronary artery with a long occluded segment. He did well post catheterization and was discharged on Day 28. He elected to withdraw from the study on Day 34; no reason was specified. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.
[*Reviewer's note: The sponsor did not consider this treatment emergent for the integrated analysis of safety. I agree. The event occurred fifteen days after his last dose of study drug. I did not add the latter event to the listing of treatment emergent adverse events.*]

Subject 12701/221300 [TL 022]
SAE: viral infection NOS
A 34 year old woman received her last dose of ramelteon 16 mg on Day 121. On Day 123, she was hospitalized for treatment of fever, weakness and chest discomfort. She was noted to tachycardic, tachypneic, hypotensive and febrile upon admission to the intensive care unit. She was given intravenous antibiotics as well as rehydration. She was discharged from the hospital on Day 126 and discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12704/221505 [TL 022]
SAE: brain neoplasm
A 49 year old woman with no significant past medical history was found to have a limp and left-sided hemiparesis on study Day 50. MRI of the brain revealed a non-enhancing intra-axial lesion that was centered within the ventral medulla and extended into the lower pons and cervicomedullary junction. A small ventral exophytic component was noted. She was discontinued from the study having received her last dose of ramelteon 16 mg on Day 54. The adverse events were noted to be continuing at her last clinic visit on Day 103. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12708/221151 [TL 022]
SAE: coronary artery occlusion
A 61 year old woman, with a past medical history significant for hyperlipidemia, coronary artery disease, pulmonary artery hypertension, left ventricular diastolic dysfunction as well as pulmonic and tricuspid regurgitation, was discontinued from the study having received her last dose of ramelteon 16 mg on Day 22. On Day 23, she was hospitalized for stent placement to treat an occluded left anterior descending coronary artery. She did well post operatively and was discharged on Day 24. She was discontinued from the study due to this hospitalization. This adverse event was probably not related to use of study drug.

Subject 12646/222118 [TL 022]
SAE: cervical myelopathy with peripheral neuropathy
A 73 year old man, with no significant past medical history, was receiving ramelteon 8 mg. On Day 174, he became disabled due to peripheral neuropathy. On Day 225, during a study visit, he was noted to be using a walker for stability after having fallen twice due to weakness. He took his last dose of study medication on Day 224; he was withdrawn from the study due to this SAE. This adverse event was probably not related to use of study drug.

Subject 12817/221265 [TL022]
SAE: prolactinoma
A 29 year old G_0P_0, was receiving ramelteon 16 mg. On [ ] she had a prolactin level of 114.4 (normal range is 2.8-29.2 ng/ml). Study medication was stopped on [ ] study Day 228, due to the elevated prolactin level. On [ ] she had a MRI scan of her head. This study was notable for an asymmetric pituitary gland consistent with a pituitary adenoma. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10211/252463 [TL 025]
SAE: atrial fibrillation
A 79 year old woman, with past medical history notable for atrial fibrillation, received her last dose of placebo on Day 20. On Day 21 she was hospitalized for treatment of atrial fibrillation. She was discontinued from the study due to "the length of interruption of the study drug." This adverse event was probably not related to use of study drug.

Subject 12634/251830 [TL 025]
SAE: transient ischemic attack
A 72 year old woman, with past medical history significant for coronary artery disease, atrial fibrillation, hypertension, migraine headaches and congestive heart failure, received her last dose of ramelteon 8 mg on Day 10. On Day 11, she complained of blurred vision and was found to be disoriented. Upon evaluation in the emergency room, she was food to have mild hypertension as well as an abnormal electrocardiogram: sinus bradycardia (47 bpm) with 1st degree atrioventricular block (236 ms); left axis deviation; left ventricular hypertrophy with QRS widening (114 ms); inferior myocardial infarction of undetermined age. She was released on the same day; she was withdrawn from the study due to this event. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20738/251509 [TL 025]
SAE: cellulitis, atrial fibrillation, dehydration, hyponatremia
An 88 year old woman, with past medical history significant for atrial fibrillation, septal wall myocardial infarction, mitral valve prolapse, palpitation, hypertension, was receiving ramelteon 8 mg. On Day 38, she began complaining of nausea, diarrhea, abdominal pain, dizziness, generalized weakness and slight confusion. She received her last dose of ramelteon on Day 38. On Day 42 she was hospitalized for treatment of atrial fibrillation, cellulitis, dehydration, hypoalbuminemia (albumin of 2.6) and hyponatremia (serum sodium of 124). She recovered from all the adverse events, except the atrial fibrillation, by Day 45. Her atrial fibrillation was ongoing as of Day 57 when she was withdrawn from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 21383/321317 [TL 032]
SAE: internal hernia
A 44 year old woman, with no significant past medical history, received ramelteon 16 mg through Day 96. On that day she had acute onset lower abdominal pain associated with anorexia, nausea and emesis. A CT scan of her abdomen revealed a fairly high-grade small bowel

obstruction thought to be secondary to an internal hernia and infarction of the small intestine. She was withdrawn from the study due to this event. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Table 23: SAE leading to discontinuation grouped by system organ class (SOC)

Cardiac disorders			
	Angina unstable	16 mg	12701/221049
	Atrial fibrillation	8 mg	20738/251509
	Coronary artery occlusion	16 mg	12700/211084
	Coronary artery occlusion	16 mg	12708/221251
	Coronary atrial fibrillation aggravated	Placebo	10211/252463
Gastrointestinal disorders			
	Internal hernia	16 mg	21383/321317
General disorders and administration site conditions			
	Chest discomfort, chest pain	16 mg	12700/211084
Infections and infestations			
	Pneumonia NOS	8 mg	12676/222031
	Cellulitis	8 mg	20738/251509
	Viral infection NOS	16 mg	12701/221300
Metabolism and nutrition disorders			
	Dehydration	8 mg	20738/251509
	Hyponatraemia	8 mg	20738/251509
Neoplasms benign, malignant and unspecified			
	Brain neoplasm NOS	16 mg	12704/221505
	Colon cancer NOS	8 mg	12074/170154
	Prolactinoma	16 mg	12817/221265
Nervous system disorders			
	Carotid artery stenosis	16 mg	12700/211084
	Cerebrovascular accident	8 mg	12651/222003
	Convulsions NOS	16 mg	12815/201725
	Transient ischaemic attack	8 mg	12634/251830
	Cervical myelopathy with peripheral Neuropathy	8 mg	12646/222118
Pregnancy, puerperum, and perinatal conditions			
	Ectopic pregnancy	16 mg	12676/211021
Reproductive system and breast disorders			
	Benign prostatic hyperplasia	8 mg	12657/251187
Vascular disorders			
	Deep vein thrombosis NOS	8 mg	12591/222030

(modification of table 1.b, from appendix D of the IAS)

7.1.2.2 Serious adverse events which did not lead to discontinuation

Subject 12074/2042 [TL 005]
SAE: lung cancer (stage unspecified) and syncope
A 32 year old woman had been randomized to receive the five study treatments in the following order: 8 mg ramelteon, 16 mg of ramelteon, 4 mg of ramelteon, 32 mg of ramelteon and placebo. She was hospitalized on Day 38, after receiving her last dose of medication on Day 37, due to a syncopal episode. She was found to have lung cancer. At the time of diagnosis, she was leaving to take a job in Germany. She opted to seek treatment abroad and was subsequently lost to follow-up. This adverse event was probably not related to use of study drug.

Subject 10672/201351 [TL 020]
SAE: arthritis
A 50 year old woman, with past medical history significant for arthritis, cardiac murmur, anemia and right hip replacement, received her last dose of ramelteon 16 mg on study Day 52. On Day 58, she had exacerbation of arthritis requiring left hip replacement surgery. She recovered and was discharged on Day 61. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. While I disagree, in order to be consistent with the sponsor's definition as used elsewhere, I will not add it to the list of treatment-emergent adverse events.*]

Subject 12593/202290 [TL 020]
SAE: gastrointestinal hemorrhage
A 58 year old woman, with past medical history significant for peptic ulcer disease 30 years prior, tobacco and alcohol use, noted black stools in association with nausea and poor appetite on Day 28, the last day that she took ramelteon 16 mg. On Day 31, she was hospitalized for evaluation of gastrointestinal bleeding. At the time of hospitalization, she was found to have coffee ground emesis, hypotension, occult stool blood (4+), hemoglobin of 9.2 g/dl. An upper endoscopy revealed no source for the bleeding. The bleeding resolved and the patient was discharged on Day 34. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12692/201077 [TL 020]
SAE: nausea
A 62 year old woman, whose past medical history was significant for hiatal hernia, hypercholesterolemia, and laminectomy, experienced intermittent nausea on Day 24, the last day that she took ramelteon 8 mg. On Day 35, she was hospitalized for severe nausea, intermittent substernal chest pain associated with left upper extremity tingling. Her treating physician determined that the nausea and chest pain were related to the subject's use of Niaspan. The subject recovered on Day 37. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.
[*Reviewer's note: The sponsor did not consider this treatment emergent for the integrated analysis of safety. I agree. The event occurred fifteen days after her last dose of study drug. I did not add the latter event to the listing of treatment emergent adverse events.*]

Subject 12699/201964 [TL 020]
SAE: pneumonia
A 60 year old man, with past medical history notable for gastritis, hyperlipidemia, osteoarthritis, chronic lung disease and tobacco use, was taking placebo through Day 52. On Day 57, he reported a history of weight loss, productive cough and pleuritic chest pain. He was hospitalized for what was discovered to be streptococcus pneumonia. He was discharged on Day 61. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. The event occurred within 7 days of the last dose of study drug. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 09843/221063 [TL 022]
SAE: uterine fibroids
A 47 year old woman, with a past medical history significant for endometriosis, anemia and dysfunctional uterine bleeding due to uterine fibroids, was hospitalized for a total abdominal hysterectomy with bilateral salpingo-oophorectomy on Day 52. She was discharged on Day 53. Although her use of ramelteon 16 mg was interrupted on Day 51, she continued in the study after being discharged from the hospital. This adverse event was probably not related to use of study drug.

Subject 09843/221246 [TL 022]
SAE: syncope
A 59 year old man, with past medical history significant for esopghageal reflux disease and bradycardia, was receiving ramelteon 16 mg. On Day 28, he was hospitalized after an episode of syncope. When no reason for his syncope could be found, he was discharged on Day 29. This adverse event was probably not related to use of study drug.

Subject 09843/221250 [TL 022]
SAE: gastroesophageal reflux disease
A 49 year old man, with past medical history significant for myocardial infarction, angina, and gastroesophageal reflux disease, was receiving ramelteon 16 mg. On Day 99, he was hospitalized after an episode of heartburn in association with chest pain radiating to the left shoulder and arm with numbness. He was discharged on Day 100 with the diagnosis of worsening gastroesophageal reflux disease. This adverse event was probably not related to use of study drug.

Subject 09894/222099 [TL 022]
SAE: abdominal pain NOS, ovarian cyst
A 65 year old woman, with past medical history significant for congestive heart failure, hypertension, and gastric ulcer surgery, was receiving ramelteon 8 mg. She experienced abdominal pain on Day 108 and was hospitalized. She was discharged on Day 113. On Day 119, she was hospitalized with left lower quadrant pain. Radiography revealed a complex left ovarian mass. On Day 132, she underwent exploratory laparotomy and excision of the left ovary. This adverse event was probably not related to use of study drug.

Subject 10308/222005 [TL 022]
SAE: Electrocardiogram T wave abnormality
A 77 year old man with no relevant past medical history received ramelteon 8 mg while participating in the study. He completed the study and was seen for a final visit on Day 339, three days after his last dose of study medication. At that visit, he was noted to have an ECG that showed sinus tachycardia with a marked T wave abnormality. He underwent angioplasty on Day 342 and was discharged on Day 343. While there is no clear causal correlation, it is not possible to completely rule out an association with use of the study medication.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. The event occurred within 7 days of the last dose of study drug. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 10308/222065 [TL 022]
SAE: upper abdominal pain NOS
A 77 year old woman with past medical history significant for diabetes mellitus received ramelteon 8 mg. She was hospitalized due to severe stomach pain on Day 89. An abdominal x-ray revealed an ileus in the right upper quadrant. The symptoms improved after a bowel movement. While there is no clear causal correlation, it is not possible to completely rule out an association with use of the study medication.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. The event occurred while the patient was still enrolled on the study, insofar as may be determined. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 10420/221292 [TL 022]
SAE: bladder prolapse
A 63 year old woman, with past medical history significant for bladder prolapse, was receiving ramelteon 16 mg. On Day 166 she was hospitalized for surgical repair of a partial prolapsed bladder. She was discharged on Day 168. This adverse event was probably not related to use of study drug.

Subject 14232/221347 [TL 022]
SAE: cholelithiasis
A 54 year old woman with a past medical history significant for gastroesophageal reflux disease received ramelteon 16 mg until Day 24 when the medication was discontinued. She was hospitalized on Day 25 for cholelithiasis. She had a cholecystectomy on Day 26 and was treated with oxycocet and pethidine. She was withdrawn from the study due to use of exclusionary medications. This adverse event was probably not related to use of study medication.

Subject 12557/222037 [TL 022]
SAE: coronary artery stenosis, localized infection, drug hypersensitivity
A 73 year old woman, with a past medical history significant for atherosclerotic coronary vascular disease, hyperglycemia, hypercholesterolemia and hypertension, received ramelteon 8 mg. The study drug was discontinued on Day 53 when it was discovered that the patient had

been taking an exclusionary medication at the time of screening, Zyrtec. She was withdrawn from the study. On Day 54, she was hospitalized for coronary artery stenosis. She had coronary artery bypass surgery on Day 56. After a hospital course complicated by a wound infection at the donor site, and a pleural effusion, she was discharged on Day 73. This adverse event was probably not related to the use of study drug.
[*Reviewer's note: The sponsor considered only the coronary artery stenosis treatment-emergent for the integrated analysis of safety. I agree as the other AE appear to be complications of her hospital stay. I did not add the other events to the listing of treatment emergent adverse events.*]

Subject 12591/221357 [TL 022]
SAE: intestinal obstruction NOS
A 47 year old woman with a past medical history significant for hysterectomy and appendectomy received ramelteon 16 mg. On Day 44, she was hospitalized due to a small bowel obstruction and had lysis of adhesions performed the same day. She was treated with morphine and later discharged on Day 50. While study drug was temporarily interrupted, she continued in the study. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12645/201879 [TL 022]
SAE: Diverticulitis NOS
A 57 year old man, who had previously completed study 020, was receiving ramelteon 16 mg. On Day 64, he began having increasingly severe left lower quadrant pain. A CT scan showed diverticulosis in the colon. The study drug was stopped on Day 63 then restarted. This adverse event was probably not related to use of study drug.

Subject 12646/222020 [TL 022]
SAE: spinal compression fracture
A 74 year old woman, with a past medical history significant for osteoporosis, post-polio syndrome with lower back pain, hypertension, was receiving ramelteon 8 mg. On Day 272, she was found to have a compressed vertebra which was thought to be due to a fall in the bathtub on an unknown date. She underwent a kyphoplasty on Day 276. She was discharged on Day 277. The study medication was interrupted but then resumed and she stayed on the study. This adverse event was probably not related to use of study medication.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. The event occurred while the patient was still enrolled on the study, insofar as may be determined. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 12657/201781 [TL 022]
SAE: inguinal hernia NOS
A 41 year old man, who had previously completed study TL020, was receiving ramelteon 16 mg. On Day 93, he was hospitalized for worsening of a left inguinal hernia. He was subsequently discontinued from the study, having received his last dose of study drug on Day 133. This adverse event was probably not related to use of study drug.

Subject 12704/251141 [TL 022]
SAE: Bladder cancer NOS
An 83 year old man, who had previously completed study TL025, was receiving ramelteon 8 mg. His past medical history was significant for prostatectomy. On Day 169, he was hospitalized for treatment of bladder cancer. He was discharged, on Study Day 170, after a transurethral resection of the bladder tumor. Study drug was briefly interrupted during the hospital stay but the subject continued in the study. This adverse event was probably not related to use of study drug.

Subject 12709/251247 [TL 022]
SAE: Chest pain
A 72 year old woman, who had previously completed study TL025, was receiving ramelteon 8 mg. She was hospitalized on Day 90 for evaluation of non-cardiac chest pain. She had complained of chest tightness for 3 weeks prior to hospital admission. She reported that she had begun taking Actonel 4 weeks prior to admission. She noted that after taking the Actonel, she began having epigastric and chest discomfort. After a cardiac and gastrointestinal evaluation, neither of which provided a diagnosis, she was discharged on Day 91. This adverse event was probably not related to use of study drug.

Subject 12720/221110 [TL 022]
SAE: Uterine fibroids
A 48 year old woman was receiving ramelteon 16 mg. On Day 84 she was hospitalized for treatment of uterine fibroids. She was discharged on Day 85 after an elective hysterectomy. Study drug was briefly interrupted during the hospital stay but the subject continued in the study. This adverse event was probably not related to use of study drug.

Subject 12720/221110 [TL 022]
SAE: Staphylococcal infection NOS
A 51 year old woman was receiving ramelteon 16 mg. Her last dose of study drug was on Day 78. She was hospitalized with a *Staphylococcus Aureus* infection of the urine on Day 81. She received a course of antibiotics and was discharged on Day 89. She was discontinued from the study due to withdrawal of consent. This adverse event was probably not related to use of study drug.

Subject 12823/221174 [TL 022]
SAE: Arthritis NOS
A 65 year old woman, with a past medical history significant for arthritis, was receiving ramelteon 16 mg. On Day 209, she was hospitalized and underwent a total right hip replacement. She was discharged to a rehabilitation facility on Day 212. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not consider this event treatment emergent for the integrated analysis of safety. I disagree. The event occurred while the patient was still enrolled on the study, insofar as may be determined. Since I consider this event treatment emergent, I have added it to the listing of treatment emergent adverse events.*]

Subject 20765/221274 [TL 022]
SAE: Chest pain
A 62 year old woman was receiving ramelteon 16 mg. She took her last dose of study medication on Day 54 and then discontinued due to lack of efficacy. On Day 62 during her final visit, the ECG performed revealed significant ST-T changes compared with her previous study. She was admitted that day for evaluation of a dull intermittent substernal ache which had been present for 5 days prior to admission. After a cardiac evaluation, which revealed normal coronary arteries with a normal left ventricular ejection fraction, she was discharged to home on Day 64 with no further complaints of chest pain. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not consider this treatment emergent for the integrated analysis of safety. I agree. The event occurred eight days after her last dose of study drug. I did not add the latter event to the listing of treatment emergent adverse events.*]

Subject 20766/221592 [TL 022]
SAE: Perforated duodenal ulcer
A 56 year old woman, with past medical history significant for gastric bypass surgery and ileal bypass surgery, received her last dose of ramelteon 16 mg on Day 203. On Day 204, the subject was hospitalized after the development of right-sided abdominal pain. She was found to have a perforated duodenal ulcer with peritonitis. She was discharged on Day 214 after a laparoscopic cholescystectomy. She resumed use of study drug on Day 215. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.
[*Reviewer's note: The sponsor notes that this event occurred after the 13 April cutoff date for the data listings but before the 30 June 2004 cut-off intended for the IAS, therefore the above event does not appear in the sponsor's data listings. I have added it into the listings of adverse events in this review.*]

Subject 12812/221554 [TL 022]
SAE: Hiatal hernia
A 49 year old woman, with past medical history significant for irritable bowel syndrome and intermittent left quadrant pain, was receiving ramelteon 16 mg. On Day 243, the subject was hospitalized for a laparoscopic hernia repair with Nissan fundoplication. Study drug was interrupted on Day 238 but the subject was not withdrawn from the study. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.
[*Reviewer's note: The sponsor notes that this event occurred after the 13 April cutoff date for the data listings but before the 30 June 2004 cut-off intended for the IAS, therefore the above event does not appear in the data listings. I have added it into the listings of adverse events in this review.*]

Subject 12557/201751 [TL 022]
SAE: Worsening meniscal tear of the knee
A 57 year old woman, with past medical history significant for osteoarthritis and bilateral knee joint pain, was receiving ramelteon 16 mg. On Day 248, the subject had outpatient surgery to repair a worsening right medial meniscus tear. She continued to receive study drug. This adverse event was probably not related to use of study drug.

[*Reviewer's note: The sponsor notes that this event occurred after the 13 April cutoff date for the data listings but before the 30 June 2004 cut-off intended for the IAS, therefore the above event does not appear in the data listings. I have added it into the listings of adverse events in this review.*]

Subject 12676/211022 [TL 022]
SAE: Uterine leiomyoma
A 33 year old woman, with past medical history significant for uterine fibroids, was receiving ramelteon 16 mg. On Day 288, the subject had a myomyectomy as treatment for menorrhagia. She was discharged on Day 290 and continued in the study. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor notes that this event occurred after the 13 April cutoff date for the data listings but before the 30 June 2004 cut-off intended for the IAS, therefore the above event does not appear in the data listings. I have added it into the listings of adverse events in this review.*]

Subject 12635/251022 [TL 025]
SAE: Myocardial ischemia
A 65 year old man was receiving ramelteon 4 mg. He received his last dose of study drug on Day 45, after awakening that morning with chest and back pain. On Day 46 he presented to the emergency room with pain radiating down his left leg. An ECG performed 2 weeks prior to the first dose of study drug had revealed a septal infarct of undetermined age. He was discharged with Coumadin on Day 50. This adverse event was probably not related to use of study drug. He later withdrew from the study due to the adverse event: "restlessness."

Subject 12699/251865 [TL 025]
SAE: Jaw fracture
An 83 year old woman was receiving placebo. On Day 6, she tripped and fell fracturing her jaw. She was discharged on Day 8 after a surgical repair of her jaw. She continued in the study after her jaw repair. This adverse event was probably not related to use of study drug.

Subject 12707/251231 [TL025]
SAE: Arthritis NOS
A 78 year old man, with a past medical history significant for chronic left shoulder arthritis, 6 coronary artery bypass grafts, and an irregular heartbeat, was randomized to ramelteon 8 mg. On Day 15, he reported intermittent arm and shoulder pain. He was hospitalized on Day 15 for a cardiac evaluation. He was discharged on Day 16 with no cardiac etiology for his symptoms found. This adverse event was probably not related to use of study drug.

Subject 20384/251480 [TL 025]
SAE: amnesia
A 78 year old man, with a past medical history significant for sinus bradycardia, prostate cancer, diabetes and anemia, was randomized to ramelteon 4 mg. On Day 32, he was hospitalized for "amnesia due to bradycardia." His blood pressure was 210/60, with no heart rate provided.

During the hospitalization, his heart rate was stable between 48 and 54 beats per minute. He was discharged on Day 35. This adverse event was probably not related to use of study drug.

Subject 22189/252673 [TL 025]
SAE: dizziness
A 76 year old woman was randomized to placebo. Her last day of study medication was on Day 49. On Day 75, she was hospitalized for nausea and "graying" of her visual fields. She underwent a cardiac evaluation. On Day 77, she was discharged on aspirin and hydrochlorthiazide. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not consider this treatment emergent for the integrated analysis of safety. I agree. The event occurred twenty-six days after her last dose of study drug. I did not add the latter event to the listing of treatment emergent adverse events.*]

Subject 301032 [TL 030]
SAE: myocardial infarction
A 47 year old man, with known severe renal impairment as well as coronary artery disease with prior angioplasty, received a single 16 mg dose of ramelteon on Day 1, followed by daily 16 mg doses starting on Day 4. Twenty-eight days after his last dose of study drug, he was seen in the emergency room with anginal symptoms. The next day, he was hospitalized for a myocardial infarction. He was discharged after a catheterization and stent placement. The dye used for catheterization exacerbated his renal failure symptoms. This adverse event was probably not related to use of study drug.
[*Reviewer's note: The sponsor did not indicate whether these events were considered treatment-emergent for the integrated analysis of safety. Using the definition proposed by the sponsor, they would not be since they occurred more than 7 days after the last dose of study medication.*]

Subject 12925/321357 [TL032]
SAE: diverticulitis NOS
A 43 year old woman, with a past medical history significant for constipation and kidney stones, received placebo, taking her last dose of study drug on Day 69. On Day 71, she developed severe left-sided abdominal pain which caused difficulty in walking. A CT scan revealed focal thickening of the descending colon with inflammatory changes which were likely to represent focal diverticulitis. She was discharged on Day 74. This adverse event was probably not related to use of study drug.

Subject 20646/321055 [TL032]
SAE: Cholelithiasis
A 37 year old man received ramelteon 16 mg. On Day 54, he experienced an episode of hematemesis and melanic stools. On Day 63, he went to the emergency room with epigastric and right upper quadrant pain. He was admitted to the hospital and underwent a cholescystecomy on Day 65 to resect an echogenic focus along the wall of the gallbladder. The pathological record indicated that there were sections of the gallbladder which exhibited chronic inflammation. The use of study drug was temporarily interrupted. He was discharged from the hospital on Day 69. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

7.1.2.3 Reviewer's summary

There were multiple SAE reported as reasons for discontinuation, however, the types of AE reported were not unusual for a product of this class. Aside from neuropsychiatric complaints, which are common to the sedative-hypnotics, there were no other organ systems that seemed to have disproportionate amount of adverse events noted.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The table below reflects data from both the original submission (table 22.2.1.1 in the IAS) and the 120-day safety update (table 5b).

There were 3594 unique patients who received ramelteon. Some of those patients received more than one dosage strength. In the event of discontinuation, those patients were listed in both the individual dose column for the dose received at discontinuation as well as in the all doses column. It should be noted that the sum of the patients in the individual dosage strength exposure columns will therefore be higher than the all doses column.

In the following modification of Table 5a in the IAS, I have corrected some numbers that were erroneous in the sponsor's submissions, specifically the number of pregnancies and the number of deaths. Seven pregnancies are recorded in the all doses column to account for both the woman who did not receive study drug and the one who received 32 mg.

There were no discontinuations among the 181 study participants who received 64 mg of ramelteon so I have not included those patients as a separate column in the table below.

Of the patients who received 32 mg of ramelteon, only one was discontinued: protocol deviation-pregnancy. I have not included the patients who received 32 mg of ramelteon as a separate column since most of them completed the study. The one discontinuation from the 32 mg group is included in the "all doses of ramelteon" column.

One patient who was randomized to receive ramelteon was discovered to be pregnant before her first dose of study drug was ingested. I have included her in the "all doses of ramelteon" column.

At the time of the original submission and at the time of the 120 day safety update, study 022 (a long-term safety study) was ongoing since not all participants had completed, so the table below reflects only the data available at the time of database lock (20 September 2004) for the 120 day safety update. Most of the discontinuations in the 8mg and the 16 mg groups were participants in study TL022.

In the rows which list reasons for discontinuation, the percentages given are the percentage of those who discontinued who discontinued for a given reason, e.g. in the <4 mg group there were

2 discontinuations, 50% (n=1) of those had an adverse event and 50% (n=1) discontinued for "other" reasons.

Table 24: Subject disposition in Phase I to Phase III studies

		Ramelteon				
	Placebo (n=1151)	**<4 mg (n=12)**	**4 mg (n=348)**	**8 mg (n=1250)**	**16 mg (n=1961)**	**All Doses of Ramelteon (n=3594)**
Completed	1014 (88.1%)	10 (88.3%)	297(85.3%)	790 (72.1%)	868 (47.9%)	2190 (62.7%)
Discontinued	140 (13.8%)	2 (16.7%)	51 (14.7%)	244 (22.3%)	668 (36.9%)	966 (27.7%)
Adverse event	23 (16%)	1 (50%)	9 (17.6%)	47 (19.3%)	136 (20.4%)	193 (20%)
Lack of Efficacy	33 (23.5%)	0	14 (27.5%)	80 (32.8%)	186 (27.8%)	280 (29%)
Protocol deviation	23 (16.4%)	0	16 (31%)	40 (16.4%)	65 (10%)	122 (12.6%)
Withdrawal of consent	32 (22.8%)	0	8 (15.7%)	49 (20.1%)	133 (20%)	190 (19.7%)
Lost to follow-up	11 (7.8%)	0	1 (2%)	7 (2.9%)	102 (15.3%)	110 (11.4%)
Investigator discretion	3 (2.1%)	0	1 (2%)	3 (1.2%)	7 (1%)	13 (1.3%)
Death	0	0	0	0	2 (<1%)	2 (<1%)
Study termination	1 (<1%)	0	0	0	0	0
Pregnancy	4 (2.8%)	0	0	2 (1%)	3 (<1%)	7 (<1%) *
Other	10 (7.1%)	1 (50%)	2 (4%)	16 (6.6%)	34 (5%)	53 (5.5%)

7.1.3.2 Adverse events associated with dropouts

I have provided a table in order to give an overview of the type of adverse events seen during the Phase I-III trials.

An expanded version of the table below, with line listings, may be found in section 10.1 of the Appendix.

The SAE which led to discontinuation have been discussed in section 7.1.2 and are not presented again here.

Eleven women were discontinued due to pregnancy; their narratives may be found in section 7.1.14.

Since ramelteon is proposed for use as a hypnotic, I have provided a representative sample of the narratives for those patients who discontinued for adverse events commonly seen with sedative-hypnotics.

I have also, due to ramelteon's novel mechanism of action, presented a representative sample of the narratives for patients with evidence of hormonal abnormalities.

The narratives below are grouped by study.

Table 25: Discontinuations for adverse events (non-serious)

System Organ Class/ Preferred term	Number of patients
Blood and lymphatic system disorders	
Anemia NOS aggravated	1
Eosinophila	1
Neutropenia , including Neutropenia aggravated	2
Cardiac disorders	
Palpitations	2
Supraventricular extrasystoles	1
Ventricular extrasystoles	1
Ear and labyrinth disorders	
Hyperacusis	1
Labyrinthitis NOS	1
Sensation of pressure in ear	1
Vertigo	1
Endocrine disorders	
Acquired hypothyroidism	1
Adrenal insufficiency NOS	1
Thyroid nodule	1
Eye disorders	
Conjunctivitis	1
Eye irritation/eye pain	2
Photophobia	1
Vision blurred	1
Papilloedema	1
Gastrointestinal disorders	
Abdominal distention	1
Abdominal pain NOS	5
Abdominal pain upper	2
Constipation	1
Diarrhea NOS	5
Dyspepsia	1
Gastric ulcer hemorrhage	1
Gastrointestinal upset	1
Irritable bowel syndrome	1
Loose stools	1
Nausea	15
Tongue disorder NOS	1
Vomiting NOS	4

Table 25: Discontinuations for adverse events (non-serious), continued

System Organ Class/ Preferred term	Number of patients
General disorders and administration site conditions	
Fatigue	11
Headache	1
Lethargy	3
Pain NOS	1
Pyrexia	2
Feeling abnormal	1
Hepatobiliary disorders	
Hyperbilirubinemia	1
Infections and infestations	
Influenza	1
Periodontitis	1
Sinusitis	1
Urinary tract infection NOS	2
Varicella	1
Pharyngitis streptococcal	1
Pneumonia NOS	2
Immune System disorders	
Type 1 hypersensitivity	1
Injury, poisoning and procedural complications	
Laceration	1
Compression fracture	1
Metabolism and nutrition disorders	
Hypoalbuminemia	1
Hypomagnesemia	1
Dehydration	1
Neoplasms benign, malignant and unspecified	
Polyp NOS	1
Prostate cancer NOS	1
Prolactinoma	1

Table 25: Discontinuations for adverse events (non-serious), continued

System Organ Class/ Preferred term	Number of patients
Investigations	
Alanine aminotransferase increased	2
Aspartate aminotransferase increased	1
Blood alkaline phosphatase increase NOS	1
Blood corticotrophin increased	1
Blood cortisol decreased	4
Blood creatinine increased	2
Blood lactate dehydrogenase increased	2
Blood pressure increased	1
Blood prolactin increased	2
Blood testosterone decreased	1
Blood testosterone increased	1
Body temperature increased	1
Blood thyroid stimulating hormone increased	1
Blood urea increased	1
Drug screen positive	1
Heart rate increased	1
Liver function tests abnormal	1
Neutrophil count increased	2
Weight increased	2
White blood cell count increased	1
White blood cell count NOS	1
Platelet count increased	1
Vascular disorders	
Hot flushes NOS	2
Hypotension NOS	1
Arterial stenosis NOS	1

Table 25: Discontinuations for adverse events (non-serious), continued

System Organ Class/ Preferred term	Number of patients
Musculoskeletal and connective tissue disorders	
Arthralgia	1
Muscle cramps	1
Muscle spasms	1
Muscle twitching	1
Muscle weakness NOS	1
Osteoarthritis	1
Rheumatoid arthritis	1
Myalgia	1
Nervous system disorders	
Ageusia	1
Balance impaired NOS	1
Depression	1
Disturbance in attention	2
Dizziness	22
Facial palsy	1
Formication	1
Headache, including headache NOS and migraine	16
Hemiparesis	1
Increased activity	1
Jerky movement NOS	1
Memory impairment	1
Neurological disorder NOS	1
Nervousness	1
Paresthesia	3
Parosmia	1
Sedation, including somnolence	32
Sleep apnea syndrome	1
Syncope	2
Transient ischemic attack	1
Social circumstances	
Family stress NOS	1
Impaired driving ability	1
Surgical and medical procedures	
Central nervous system stimulation NOS	1

Table 25: Discontinuations for adverse events (non-serious), continued

System Organ Class/ Preferred term	Number of patients
Psychiatric disorders	
Affect lability	1
Agitation	2
Anorgasmia	1
Anxiety	4
Confusion	1
Decreased activity	1
Depression	6
Derealisation	2
Hypervigilence	1
Insomnia, including insomnia exacerbated	18
Irritability	1
Mood alteration NOS	1
Mood disorder, NOS	1
Nightmare	2
Restlessness	3
Sleep disorder NOS	1
Sleep walking	1
Somnolence	1
Tension	1
Thinking abnormal	1
Renal and urinary disorders	
Azotemia	1
Calculus renal NOS	1
Difficulty in micturition	1
Proteinuria	1
Renal failure NOS	1
Reproductive system and breast disorders	
Amenorrhea NOS	1
Erectile dysfunction NOS	1
Menorrhagia	1
Menstruation irregular	1
Priapism	1

Table 25: Discontinuations for adverse events (non-serious), continued

System Organ Class/ Preferred term	Number of patients affected
Respiratory, thoracic and mediastinal disorders	
Chronic obstructive airways disease	1
Cough	1
Dyspnea NOS	1
Pleurisy	1
Emphysema	1
Skin and subcutaneous tissue disorders	
Alopecia	1
Pruritis NOS	2
Rash erythematous	1
Rash generalized	1
Rash maculo-papular	1
Rash NOS	4
Sweating increased	1
Urticaria NOS	1

7.1.3.2.1 Discontinuations from Study TL020

Subject 10153/201133

Adverse events: azotemia, abnormal liver function tests

A 57 year old woman received her first dose of placebo on 10 April 2003. At baseline her ALT was 18 U/L, AST was 21 U/L, BUN was 7.9 mmol/L and creatinine was 97 micromol/L. On the final measurement before discontinuation, ALT was 92, AST was 64, BUN was 7.9 and her creatinine was 133. She was discontinued from the study on Day 19 and was found to have recovered, without treatment, on Day 29. There is probably no correlation with use of study drug.

Subject 10153/201653

Adverse event: weakness

A 43 year old woman, with past medical history significant for insomnia and seasonal allergies, was randomized to ramelteon 16 mg. On Day 2, she experienced weakness. She received her last dose of study drug on Day 3 and was discontinued from the study. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12635/201054

Adverse event: restlessness

A 47 year old man was randomized to ramelteon 16 mg. On Day 27, he experienced inner restlessness. He received his last dose of study drug on Day 28 and was discontinued from the study. He recovered on Day 29 without treatment. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 126533/201865
Adverse event: dizziness/vomiting
A 33 year old man was randomized to placebo. On Day 14, he experienced dizziness and vomiting. He received his last dose of study drug on Day 14 and was discontinued from the study. His symptoms resolved on Day 15 without treatment. This adverse event was probably not related to use of study drug.

Subject 12692/201077
Adverse events: diarrhea, nausea
This subject had an SAE which has been previously discussed in detail. The adverse events listed here are the ones that led to discontinuation. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12695/201319
Adverse events: somnolence, dizziness, photophobia, muscle twitching, hyperacusis
A 41 year old man, with past medical history only notable for insomnia, was receiving ramelteon 16 mg. On Day 8 he complained of feeling "groggy." On Day 14, he complained of dizziness, muscle twitching, photophobia and hyperacusis. He received his last dose of study drug on Day 14 and was discontinued from the study. He recovered without treatment over 4 weeks after study completion. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12719/202348
Adverse events: depression, fatigue, memory impairment and eye pain
A 44 year old man, whose past medical history was significant for insomnia, was receiving ramelteon 16 mg. On Day 8, he complained of depression, fatigue, loss of memory and eye pain. He received his last dose of study medication on Day 13 and was discontinued from the study. He recovered without treatment on day 14. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12723/201297
Adverse events: insomnia (exacerbated), syncope, paresthesia, parosmia, eye irritation
A 54 year old woman, with past medical history significant for insomnia and fibromyalgia, was randomized to ramelteon 16 mg. On Day 8, she experienced worsening insomnia. On day 18, she felt faint. On Day 19, she has paresthesias of the distal extremities and was sensitive to smell. On Day 20, she had burning eyes. She took her last dose of study drug on Day 21 and was discontinued. She recovered from the eye pain on Day 21. She recovered from all other symptoms except the exacerbated insomnia on Day 37. The latter symptom was ongoing. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12723/201299
Adverse events: insomnia exacerbated, difficulty in micturition
A 63 year old man was receiving placebo. On Day 8 and Day 9, he experienced difficulty urinating as well as worsening insomnia. He received the last dose of study drug on Day 10 and was discontinued from the study. His difficulty in micturition was resolved on Day 11 without treatment. His exacerbation of insomnia was treated by an increase in zolpidem dosing. This adverse event was probably not related to use of study drug.

Subject 12813/201261
Adverse event: somnolence
A 63 year old woman was randomized to ramelteon 8 mg. On Day 12 she experienced grogginess. She received her last dose on Day 11 and was discontinued from the study. She recovered from this adverse event on Day 14 without treatment. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12813/201262
Adverse events: nausea, somnolence, headache NOS, insomnia
A 39 year old woman was randomized to ramelteon 16 mg. On Day 1 she experienced nausea. She received her last dose of study medication on Day 2 and discontinued from the study. On Day 3, she experienced worsening grogginess and headache. On Day 13, she had exacerbation of her insomnia symptoms. While there is no clear causal correlation, it is not possible to entirely rule out an association with use of study drug.

Subject 12815/201725
Adverse events: hypomagnesemia, nausea, migraine NOS
This subject had two SAE which have been previously discussed in detail. The adverse events listed are the ones that led to discontinuation.

Subject 12910/201529
Adverse event: headache
A 47 year old woman was randomized to ramelteon 8 mg. On Day 9, she experienced headache and was discontinued from the study. She recovered from the adverse event on Day 16 without treatment. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12910/201530
Adverse event: anxiety
A 34 year old woman was randomized to placebo. She experienced anxiety on Day 15. She received her last dose of study medication that day and was discontinued from the study. This adverse event was probably not related to use of study drug.

Subject 20370/201434
Adverse event: Abdominal pain NOS
A 40 year old woman was randomized to ramelteon 8 mg. On Day 5, she experienced severe abdominal pain, which was treated with midazolam. She recovered from that adverse event on

Day 7. She received her last dose of study medication on Day 11 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20373/201361
A 52 year old woman was randomized to ramelteon 16 mg. On Day 16, she experienced anorgasmia. She received her last dose of study medication on Day 16 and was discontinued from the study. This adverse event was probably not related to use of study drug.

Subject 20374/201423
Adverse events: nausea, somnolence
A 46 year old woman was randomized to ramelteon 16 mg. On Day 14, she experienced nausea. On Day 15, she experienced what was described as "all day grogginess". She received her last dose of study drug on Day 16 and was discontinued form the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20756/202241
Adverse events: derealisation, sedation
A 44 year old woman was randomized to ramelteon 8 mg. On day 17, she experienced sedation and felt "unreal." She received her last dose of study drug on Day 18 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

7.1.3.2.2 Discontinuations from Study TL021

Subject 12724/211302
Adverse event: alanine aminotransferase increased
A 44 year old woman was randomized to ramelteon 16 mg. At initial screening, her ALT was 32 U/L (normal range 6-43 U/L). On Day 1, her ALT was 66 U/L. On Day 15, her ALT increased to 122 U/L. She received her last dose of study drug on Day 19 and was discontinued from the study that day. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12769/211349
A 21 year old man was randomized to ramelteon 8 mg. On Day 1 he had an exacerbation of hyperbilirubinemia. He received his last dose of study drug on day 2 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12769/211131
A 57 year old woman was randomized to ramelteon 8 mg. She received her last dose of study drug on Day 35. On Day 37, she had an episode of syncope for which she was treated by emergency medical services. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

7.1.3.2.3 Discontinuations from Study TL025

Subject 12634/251830
Adverse event: transient ischemic attack
This subject had an SAE which has been previously discussed in detail. The adverse event listed is the one that led to discontinuation.

Subject 12635/251002
Adverse event: restlessness
This subject had an SAE which has been previously discussed in detail. The adverse event listed is the one that led to discontinuation.

Subject 12682/251147
Adverse event: somnolence
An 81 year old woman was randomized to ramelteon 8 mg. On Day 2 she experienced daytime somnolence. She received her last dose of study drug on Day 7 and was discontinued form the study. She recovered from the adverse event on Day 8. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12682/251150
A 72 year old woman was randomized to ramelteon 4 mg. On Day 1 she experienced daytime somnolence. She received her last dose of study drug on Day 3. She recovered from the adverse event on Day 4. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12695/251574
Adverse events: derealisation, insomnia exacerbated, dizziness
An 82 year old woman was randomized to ramelteon 8 mg. On day 1 she complained of feeling unreal, worsening insomnia, and feeling lightheaded. She recovered from the adverse events on Day 2. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12725/251039
Adverse events: confusion, somnolence, impaired driving ability
An 84 year old woman was randomized to ramelteon 8 mg. On day 26 she complained of confusion, grogginess and impaired driving judgment. She received her last dose of study drug on Day 25 and was discontinued from the study. The confusion cleared on Day 26. The other adverse events cleared on Day 27. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12728/251367
Adverse event: facial palsy
A 71 year old man was randomized to placebo. On Day 5 he was discovered to have Bells' palsy. He received his last dose of study drug on Day 7 and was discontinued form the study. He was treated with prednisone and recovered from the adverse event on Day 22. This adverse event was probably not related to use of study drug.

Subject 12766/251364
Adverse event: dizziness
A 65 year old woman was randomized to ramelteon 4 mg. On Day 2 she complained of dizziness. She received her last dose of study drug on Day 6 and was discontinued from the study. She recovered from this AE on Day 8. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12813/251124
Adverse events: balance impaired NOS, dizziness, dyspnea NOS
An 80 year old man was randomized to ramelteon 4 mg. On Day 2 he complained of an inability to breathe, a feeling of dizziness and unsteadiness. He received his last dose of study drug on Day 14 and was discontinued from the study. He recovered from these adverse events on Day 18. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12813/251125
A 75 year old man was randomized to ramelteon 4 mg. On Day 10 he experienced worsening headaches. He received his last dose of study medication on day 12 and was discontinued from the study. He recovered on Day 13. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20370/251481
Adverse event: somnolence
A 74 year old man was randomized to ramelteon 8 mg. On Day 2, he complained of feeling groggy. He received his last dose of study medication on Day 14 and was discontinued from the study. He recovered from the adverse event on Day 15. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20381/251437
Adverse event: insomnia exacerbated
A 72 year old woman was randomized to placebo. On Day 5, she complained of worsening insomnia. She received her last dose of study drug on Day 4 and was discontinued from the study. The adverse event was ongoing as of Day 13. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20381/252201
A 71 year old man was randomized to ramelteon 8 mg. On Day 18, he complained of worsening insomnia. He received his last dose of study drug on Day 21 and was discontinued from the study. The adverse event was ongoing as of his last visit, Day 22. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20733/252176
Adverse events: nausea, vertigo, increased heart rate
A 66 year old woman was randomized to placebo. On Day 10, she complained of nausea and vertigo. On Day 11, she complained of an increased heart rate. She received her last dose of

study medication on Day 11 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20738/251507
Adverse event: lethargy
A 74 year old man was randomized to placebo. On Day 10, he complained of lethargy. He received his last dose on Day 12 and was discontinued from the study. He recovered from the adverse event on day 13. This adverse event was probably not related to use of study drug.

Subject 20738/251509
Adverse event: abdominal pain NOS, diarrhea NOS, dizziness, hypoalbuminemia, urinary tract infection NOS.
This subject had SAE which have been previously discussed in detail. The adverse events listed are the ones that led to discontinuation.

Subject 20741/251588
Adverse event: insomnia exacerbated
A 77 year old woman was randomized to placebo. On Day 2 she experienced worsening of her insomnia. She received her last dose of study drug on Day 7 and was discontinued from the study. She recovered from the adverse event on Day 10. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 21121/252682
Adverse event: somnambulism
A 77 year old man was randomized to placebo. On Day 8, he was noted to be sleepwalking. He received his last dose of study drug on Day 8 and was discontinued from the study. He recovered from the adverse event on Day 9. This adverse event was probably not related to use of study drug.

7.1.3.2.4 Discontinuations from TL022 (a 12-month open label study)

Subject 09843/222047
Adverse event: insomnia exacerbated
A 66 year old woman, who was receiving ramelteon 8 mg, experienced an exacerbation of her insomnia on Day 3. She received her last dose of study drug on Day 7 and was discontinued from the study. The adverse event resolved on Day 13.

Subject 10216/201745
Adverse events: anemia NOS aggravated and neutropenia aggravated
A 47 year old woman who had previously participated in study TL020 was randomized to ramelteon 16 mg. Her past medical history was notable for anemia, lymphocytosis and worsening neutropenia. On Day 9, she was noted to have worsening anemia and neutropenia. She received her last dose of study drug on Day 9 and was discontinued from the study. She was treated with erythropoietin but the adverse events were ongoing on Day 15 with RBC and neutrophils still below normal range, 3.6 TI/L and 1.78 GI/L. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10308/201573
Adverse event: dizziness
A 63 year old woman who had previously completed TL020 was randomized to ramelteon 16 mg. On Day 10, she was noted to have dizziness. This adverse event resolved on Day 19. She received her last dose of study drug on Day 2 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10355/221302
Adverse event: hypervigilence
A 46 year old man was assigned to ramelteon 16 mg. On Day 1, he experienced increased alertness. This resolved on Day 2. On Day 3, he again experienced increased alertness. He received his last dose of study medication on Day 2 and was discontinued form the study. The adverse event resolved on Day 3. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10365/201028
Adverse events: formication, insomnia exacerbated
A 50 year old man, who had previously completed TL020, was assigned to ramelteon 16 mg. On Day 2, he noted formication and an exacerbation of his insomnia. He received his last dose of study drug on Day 2 and was discontinued from the study. The sensation of formication dissipated on Day 4. However, the increased insomnia was ongoing at the last visit on Day 8. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10365/201297
Adverse event: sensation of pressure in both ears
A 49 year old woman who had previously completed TL020 was assigned to receive ramelteon 16 mg. On Day 1, she complained of the sensation of bilateral ear pressure. She received her last dose of study drug that day and was discontinued from the study. The adverse events resolved the same day. This adverse event was probably not related to use of study drug.

Subject 10470/17007
Adverse event: fatigue
An 81 year old man, who had previously completed TL017, was assigned to ramelteon 8 mg. On day 2 he experienced fatigue. He received his last dose of study drug on Day 7 and was discontinued from the study. This adverse event was ongoing at the last study visit on Day 8. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10470/211097
Adverse events: disturbance in attention, somnolence
A 40 year old man who had previously completed TL021 was assigned to ramelteon 16 mg. On Day 2, he experienced a lack of concentration and sleepiness. He received his last dose of study drug on Day 1 and was discontinued from the study. The adverse events resolved on Day 2.

While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10470/211100
Adverse event: erectile dysfunction
A 42year old man who had previously completed Tl021 was assigned to ramelteon 16 mg. On Day 102, he noted impotence. He received his last dose of study medication on Day 156 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10470/211371
Adverse event: fatigue
A 24 year old man who had previously completed TL021 was assigned to ramelteon 16 mg. On Day 51, he complained of fatigue. He received his last dose of study drug on Day 113 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10470/221035
Adverse event: nightmare
A 60 year old man who was assigned to ramelteon 16 mg experienced a vivid nightmare on Day 2. He received his last dose of study drug on Day 3 and was discontinued from the study. The adverse event resolved on Day 4. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10734/221142
A 61 year old man was assigned to ramelteon 16 mg, experienced sleeplessness on Day 4. He received his last dose of study drug on Day 7 and was discontinued. The adverse event resolved on Day 10. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20792/251297
Adverse event: somnolence
An 81-year-old woman, who had previously completed TL 025, was assigned to ramelteon 8 mg. On Day 2, she experienced somnolence. She received her last dose of study medication on Day 3 and was discontinued from the study. The adverse event resolved on Day 5. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 10904/222070
Adverse event: adrenal insufficiency NOS
A 68-year-old man, who had been assigned to ramelteon 8 mg, was found to have adrenal insufficiency on Day 57. His morning serum cortisol level was 55 nmol/L, with the normal range being 138-442 nmol/L. He received his last dose of study medication on Day 57 and was discontinued from the study. An adenocorticotrophic hormone stimulation test was done. The serum cortisol level was within the normal range, 221 nmol/L, at the final visit. While there is

not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12065/221073
Adverse events: dizziness, fatigue, muscle weakness NOS, headache NOS
A 42-year-old woman, who was receiving ramelteon 16 mg, complained of lassitude, muscle weakness, dizziness and morning headaches on day 2. She received her last dose of study drug on Day 10 and was discontinued from the study. The adverse events resolved on Day 13. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12104/221119
Adverse event: somnolence
A 41-year-old man, who was receiving ramelteon 16 mg, complained of daytime sleepiness on Day 2. He received his last dose of study drug on Day 10 and was discontinued from the study. The adverse event resolved on Day 12. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12432/221011
Adverse events: abnormal liver function tests
A 27-year-old man, who was assigned to ramelteon 16 mg was noted to have elevated LFTs on day 9: ALT 118 U/L, AST 479 U/L, and LDH 828 U/L. At baseline his levels were 15, 26 and 157 respectively. He received his last dose of study drug on Day 15 and was discontinued from the study. On Day 16 his ALT was 87 U/L, his AST was 86 U/L and his LDH was 193 U/L. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12432/221024
Adverse events: ageusia, paresthesia, tongue disorder NOS, vision blurred
A 50-year-old woman, who was receiving ramelteon 16 mg, noted blurred vision, "a thick-feeling tongue with a pins-and-needles sensation," a well as an inability to taste on Day 1. She received her last dose of study drug on Day 17 and was discontinued from the study. The adverse events resolved on Day 21. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12432/221026
A 52-year-old man, who was receiving ramelteon 16 mg, complained of morning drowsiness on Day 2. He received his last dose of study drug on Day 7 and was discontinued from the study. His concomitant medications included zolpidem. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12432/221148
A 64-year-old woman, who was receiving ramelteon 16 mg, experienced morning drowsiness on day 2. She received her last dose of study drug on Day 1 and was discontinued from the study.

The adverse event resolved on Day 3. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12550/221559
A 47-year-old woman, who was receiving ramelteon 16 mg, complained of nausea and headache on Day 2. She received her last dose of study drug on Day 3 and was discontinued from the study. The nausea was improving on Day 4 but the headache was ongoing on Day 8. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 125522/170063
Adverse events: anxiety, dizziness, fatigue, feeling abnormal
A 66-year-old man, who had previously completed TL017, was receiving ramelteon 8 mg. On Day 2, he complained of fatigue, dizziness, "nocturnal awakenings with anxiety" and feeling abnormal. He received his last dose of study drug on day 17 and was discontinued from the study. The adverse events resolved on Day 18. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12552/170143
Adverse event: blood testosterone decreased
A 67-year-old man, who had previously completed TL017, was assigned to ramelteon 8 mg. On Day 106, he was noted to have decreased free testosterone (<6.5 pg/ml, normal 52-280 pg/mL) and low total testosterone (<50 pg/mL, normal 350-1030 pg/mL). This resolved on Day 114. He received his last dose of study drug on Day 125 and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12554/221121
A 64-year-old woman, who was receiving ramelteon 16 mg, experienced dizziness on Day 2. She received her last dose of study drug on Day 4 and was discontinued from the study. This adverse event resolved on day 6. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12556/201920
Adverse event: somnolence
A 33 year old woman, who had previously completed TL020, experienced daytime drowsiness on day 2. On Day 56, she took her last dose of study drug and was discontinued from the study. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12557/201752
Adverse event: dizziness
A 53 year old woman, who had previously completed TL020, was receiving ramelteon 16 mg. On day 111, she experienced dizziness. She received her last dose of study drug on Day 111 and was discontinued from the study. The adverse event was ongoing as of the last visit on Day 127.

While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12588/201958
A 63-year-old woman, who had previously completed TL020, was assigned to ramelteon 16 mg. On Day 56, she experienced restlessness. She received her last dose of study medication on Day 73 and was discontinued from the study. The adverse event resolved on Day 76. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12588/221416
Adverse events: agitation, depression, insomnia exacerbated
A 58-year-old woman, who was receiving ramelteon 16 mg, complained of agitation, depression and increased insomnia on Day 2. She received her last dose of study medication on Day 5 and was discontinued from the study. The adverse events resolved on Day 6. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12635/201803
A 32 year old woman, who had previously participated in TL020, was receiving ramelteon 16 mg. On Day 31, she complained of a "drugged feeling upon awakening". She received her last dose of study drug on Day 36 and was discontinued from the study. The adverse events resolved on Day 43. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12635/251005
Adverse event: anxiety
A 76-year-old woman, who had previously completed TL025, was assigned to ramelteon 8 mg. On Day 1 she experienced anxiety. She received her last dose of study drug on Day 1 and was discontinued from the study. The adverse event resolved on Day 1.

Subject 12646/221175
Adverse event: somnolence
A 62 year-old woman who was receiving ramelteon 16 mg complained of afternoon fatigue on Day 3. She received her last dose of study drug on Day 35 and was discontinued from the study. The adverse event resolved on Day 37. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12649/201951
Adverse event: abnormal thinking
A 41-year-old man, who had previously completed TL020, was assigned to ramelteon 16 mg. On Day 7, he had a period of abnormal thinking. He received his last dose of study medication on Day 19 and was discontinued from the study. This adverse event was ongoing at the last visit on Day 22. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12651/221007
Adverse event: affect lability
A 38-year-old woman, who was receiving ramelteon 16 mg, noted emotional lability on Day 24. She received her last dose on Day 38 and was discontinued from the study. The adverse event resolved on Day 38. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject: 12651/222092
Adverse event: lethargy
A 70-year-old man, who was receiving ramelteon 8 mg, experienced lethargy on Day 2. He received his last dose of study medication on Day 28 and was discontinued from the study. This adverse event resolved on Day 29. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12654/211057
Adverse event: headache
A 61-year-old woman, who had previously completed TL021, experienced headache on Day 2. She received her last dose of study drug on Day 1 and was discontinued from the study. The adverse event resolved on Day 2. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12655/221323
Adverse event: somnolence
A 48-year-old woman, who was receiving ramelteon 16 mg, complained of somnolence on Day 9. She received her last dose of study drug on Day 15 and was discontinued from the study. The adverse event resolved on Day 17. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12657/201151
Adverse event; acquired hypothyroidism
A 56-year-old man, who had previously participated in TL020, was found to have an elevated thyroid level on Day 57 (TSH level of 6.93 mU/L, normal 0.32-5 mU/L). He received his last dose of study drug on Day 84 and was discontinued from the study. At his last visit on Day 85, his TSH was 5.99 mU/L. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12657/201748
Adverse event: somnolence
A 62-year-old woman, who had previously completed TL020, was assigned to ramelteon 16 mg. On Day 2 she complained of afternoon drowsiness. She received her last dose of study drug on Day 8 and was discontinued from the study. The adverse event resolved on Day 11. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12661/251205
An 85-year-old woman, who had previously completed TL025, was assigned to ramelteon 8 mg. On Day 41, she experienced fatigue. She received her last dose of study drug on Day 12 9and was discontinued form the study. The adverse event resolved on Day 131. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12662/222084
Adverse events: hypotension, jerky [leg] movement NOS, nervousness
A 67-year-old woman, who was assigned to ramelteon 8 mg, complained of jerky leg movement, nervousness, and hypotension on Day 1. She received her last dose of study drug on Day 3 and was discontinued. All adverse events had resolved by Day 5. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12671/20161
Adverse events: priapism, [nocturnal] tension, headache
A 59-year-old man who had previously completed TL020 was assigned to ramelteon 16 mg. On day 1, he noted nocturnal tension and priapism. On day 2 he noted headache. He received his last dose of study medication on Day 3 and was discontinued from the study. All adverse events had resolved by Day 5. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12672/01660
Adverse event: sedation
A 60-year-old woman, who had previously completed TL020, was assigned to ramelteon 16 mg. On Day 3, she was noted to have excessive sedation. She received her last dose of study drug on Day 5 and was discontinued from the study. Her adverse event resolved on Day 8. This adverse event was probably related to use of study drug.

Subject 12682/221463
Adverse events: nausea, somnolence
A 62 year old woman, who was randomized to ramelteon 16 mg, complained of nausea and daytime somnolence on Day 1. She received her last dose of study drug on Day 4 and was discontinued from the study. The adverse events resolved on day 4. This adverse event was probably related to use of study drug.

Subject 12693/201737
Adverse event: depression
A 50 year old woman, who had previously completed TL020, was receiving ramelteon 16 mg. On Day 11, she began to complain of depression. She received her last dose of study drug on Day 31 and was discontinued from the study. This adverse event remained unchanged when she was last seen on Day 46. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12703/201220
Adverse event: menorrhagia, irregular menstruation
A 35 year old woman, who had formerly participated in study TL020, was randomized to ramelteon 16 mg. On day 13 she experienced heavy and irregular menstrual bleeding. She received her last dose of study drug on Day 17 and was discontinued from the study. These adverse events were ongoing as of her last visit on Day 32. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12704/221505
Adverse events: abnormal gait, [left] hemiparesis
This patient also had a SAE which has been described above. The listed adverse events were the ones which led to discontinuation.

Subject 12708/221002
A 29 year old man, who was receiving ramelteon 16 mg, complained of daytime fatigue on Day 128. He received his last dose of study medication on Day 140 and was discontinued from the study. The adverse event resolved on Day 143. This adverse event was probably related to use of study drug.

Subject 12708/221002
A 63-year-old woman, who was receiving ramelteon 16 mg, complained of dizziness on Day 18. She received her last dose of study drug on Day 23 and was discontinued from the study. Her symptoms resolved on Day 25. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.
[*Reviewer's note: This patient is reported as subject # 221002 in the narrative. A review of her case report forms reveals that the actual subject number is 221254.*]

Subject 12710/211010
Adverse event: fatigue
A 27 year old woman, who had previously participated in TL021, was receiving ramelteon 16 mg. On Day 57, she experienced fatigue. She received her last dose of study drug on Day 92 and was discontinued from the study. The adverse event resolved on Day 95. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12714/221314
Adverse events: lethargy, central nervous system stimulation NOS, somnolence
A 48 year old man was receiving ramelteon 16 mg. On Day 10, he complained of lethargy and "central nervous system stimulation." On Day 11, he complained of somnolence. He received his last dose of study drug on Day 10 and was discontinued from the study. This adverse event was probably related to use of study drug.

Subject 12714/251083
Adverse events: nausea, vomiting, dizziness
A 90 year old woman, who had previously completed TL025, was receiving ramelteon 8 mg. On day 2, she experienced nausea, vomiting and dizziness. She received her last dose of study drug

on Day 2 and was discontinued from the study. Only the dizziness was ongoing at the last clinic visit on Day 5. This adverse event was probably related to use of study drug.

Subject 12720/221514
Adverse events: nausea, dizziness
A 59-year-old woman was receiving ramelteon 16 mg. On Day 1 she experienced nausea and dizziness and was discontinued from the study. The symptoms resolved the next day. This adverse event was probably related to use of study drug.

Subject 12724/211476
Adverse event: Headache NOS aggravated
An 18 year old woman, who had previously completed TL021, complained of headache on Day 91. She received her last dose of study medication on Day 97 and was discontinued from the study. This adverse event was probably related to use of study drug.

Subject 12766/210329
Adverse events: nausea, dizziness
A 55 year old woman who had previously completed TL020 complained of nausea and dizziness on Day 2. She was received her last dose of study drug on Day 3 and was discontinued from the study. The adverse events resolved on Day 5. This adverse event was probably related to use of study drug.

Subject 12812/221071
Adverse event: disturbance in attention
A 55 year old man, who was receiving ramelteon 16 mg, complained of difficulty concentrating on Day 1. He received his last dose of study drug on Day 21 and was discontinued from the study. His adverse event resolved on Day 23. This adverse event was probably related to use of study drug.

Subject 12820/201253
Adverse event: paresthesia
A 36 year old woman, who had previously completed TL020, complained of occipital paresthesiae on Day 1. She received her last dose of study drug on Day 17 and was discontinued from the study. The adverse event resolved on Day 21. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12826/221053
Adverse event: depression
A 22 year old woman was receiving ramelteon 16 mg. On Day 246 she complained of depression. She received her last dose of study medication on Day 259 and was discontinued from the study. The adverse event was ongoing when she was last seen on Day 260. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12863/221040
Adverse event: nightmare
A 42 year old man was receiving ramelteon 16 mg. On Day 86, he experienced a nightmare. He received his last dose of study drug on Day 113 and was discontinued from the study. This adverse event was ongoing at the last visit on Day 113. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20765/221270
Adverse event: irritability
A 37 year old woman was receiving ramelteon 16 mg. On day 21, she complained of irritability. She received her first dose of study drug on Day 48 and was discontinued from the study. On Day 50 the adverse event resolved. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20765/221317
Adverse event: mood alteration
A 41 year old woman was receiving ramelteon 16 mg. On Day 8 she experienced mood alteration. She received her last dose of study drug on Day 16 and was discontinued from the study. The adverse event resolved on day 18. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20765/221392
Adverse event: somnolence
A 56 year old man was receiving ramelteon 16 mg. He complained of daytime somnolence on Day 14. He received his last dose of study drug on Day 14. He received his last dose of study drug on Day 28 and was discontinued from the study. The event was ongoing when he was last seen. This adverse event was probably related to use of study drug.

Subject 20765/221448
Adverse event: coded as "decreased activity"
A 64 year old woman was receiving ramelteon 16 mg. On Day 2 she complained of "worsening of ability to function during the day." She received her last dose of study drug on Day 7 and was discontinued from the study. The adverse event resolved on Day 12. This adverse event was probably related to use of study drug.

Subject 20765/221454
Adverse event: somnolence
A 61 year old woman was receiving ramelteon 16 mg. On Day 2 she complained of somnolence. She received her last dose of study drug on Day 7 and was discontinued from the study. The event resolved on Day 14. This adverse event was probably related to use of study drug.

Subject 20766/221427
Adverse events: dizziness, headache NOS aggravated
A 50 year old woman, who was receiving ramelteon, complained of dizziness and headache on Day 12. She received her last dose of study drug on Day 13 and was discontinued. The adverse events resolved on Day 13. These adverse events were probably related to use of study drug.

Subject 20766/221442
Adverse events: increased activity, insomnia
A 32 year old man was receiving ramelteon 16 mg. On Day 1, he complained of being unable to relax and experienced insomnia. He received his last dose of study drug on Day 3 and was discontinued from the study. The adverse events resolved on Day 4. This adverse event was probably related to use of study drug.

Subject 20766/2221506
Adverse event: somnolence
A 23 year old man was receiving ramelteon 16 mg. On Day 2, he complained of drowsiness. He received his last dose of study drug on Day 8 and was discontinued from the study. The adverse event resolved on day 9. This adverse event was probably related to use of study drug.

Subject 20766/221593
Adverse event: somnolence
A 55 year old man was receiving ramelteon 16 mg. On Day 10, he experienced morning drowsiness. He received his last dose of study drug on Day 86 and was discontinued from the study. The adverse event was ongoing when he was last seen. This adverse event was probably related to use of study drug.

Subject 20766/222126
Adverse event: insomnia
A 65 year old woman was receiving ramelteon 8 mg. On Day 22, she experienced insomnia. She was discontinued from the study, having had her last dose of study medication on Day 21. She was treated with alprazolam and the adverse event resolved on Day 23. This adverse event was probably related to use of study drug.

Subject 20768/221242
Adverse event: anxiety
A 60 year old woman was receiving ramelteon 16 mg. On Day 1, she experienced anxiety. She was discontinued from the study, having had her last dose of study medication on Day 4. The adverse event resolved on Day 5. This adverse event was probably related to use of study drug.

Subject 20775/221218
Adverse event: somnolence
A 37 year old man was receiving ramelteon 16 mg. On Day 2, he experienced somnolence. He was discontinued from the study, having had her last dose of study medication on Day 8. The adverse event resolved on Day 9. This adverse event was probably related to use of study drug.

Subject 20775/221312
Adverse event: dizziness
A 23 year old woman was receiving ramelteon 16 mg. On Day 36, she experienced lightheadedness. She was discontinued from the study, having had her last dose of study medication on Day 36. The adverse event resolved on Day 36. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20777/221525
Adverse event: headache NOS, dizziness, somnolence
A 53 year old man was receiving ramelteon 16 mg. On Day 2, he experienced headache. On Day 10, he complained of dizziness and AM drowsiness. He was discontinued from the study, having had his last dose of study medication on Day 16. The adverse events resolved on Day 19. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 21017/221511
Adverse event: insomnia exacerbated
A 43 year old man was receiving ramelteon 16 mg. On Day 2, he experienced an exacerbation of his insomnia. He was discontinued from the study, having had his last dose of study medication on Day 10. The adverse event resolved on Day 13. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20775/221312
Adverse event: dizziness
A 23 year old woman was receiving ramelteon 16 mg. On Day 36, she experienced lightheadedness. She was discontinued from the study, having had her last dose of study medication on Day 36. The adverse event resolved on Day 36. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 21019/221586
Adverse event: dizziness
A 55 year old woman was receiving ramelteon 16 mg. On Day 2, she experienced lightheadedness. He was discontinued from the study, having had his last dose of study medication on Day 6. The adverse event resolved on Day 7. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

7.1.3.2.5 Discontinuations from Study TL032 (a six-month safety study)

Subject 10366/321236
A 31 year old man was receiving placebo. On Day 7, he experienced fatigue, daytime drowsiness and decreased mental functioning which he attributed to lack of sleep." On Day 10, he complained of dizziness and AM drowsiness. He was discontinued from the study, having had his last dose of study medication on Day 8. The adverse events resolved on Day 14. There was no association with ramelteon.

Subject 10366/321343
Adverse event: blood prolactin increased
A 24 year old woman was receiving 16 mg of ramelteon. On Day 57, she was noted to have an elevated prolactin level, 53.6 microgram/L. She received her last dose of study drug on Day 65 and was discontinued. The event resolved on Day 65 when her prolactin level was noted to be normal. On Day 78 at followup, her prolactin level and adrenocorticotrophin levels were normal. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 12932/321106
Adverse event: amenorrhea NOS
A 19 year old woman was receiving placebo. On Day 25, she experienced amenorrhea. She took her last dose of study drug on Day 86 and was discontinued from the study. This event was probably unrelated to study drug.

Subject 20354/321139
Adverse event: somnolence
A 23 year old woman was receiving ramelteon 16 mg. On Day 7, she experienced morning somnolence. He was discontinued from the study, having had her last dose of study medication on Day 26. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20646/321145
Adverse event: blood corticotrophin increased
A 24 year old woman was receiving 16 mg of ramelteon. On Day 57, she was noted to have an elevated prolactin level, 53.6 microgram/L. She received her last dose of study drug on Day 65 and was discontinued. The event resolved on Day 65 when her prolactin level was noted to be normal. On Day 78 at followup, her prolactin level and adrenocorticotrophin levels were normal. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

Subject 20650/321042
Adverse event: blood prolactin increased, blood testosterone increased
A 28 year old man was receiving 16 mg of ramelteon. He was noted to have elevated prolactin levels on Day -20, Day 1 and Day 29. He took his last dose of study medication on Day 56. On Day 79, he was noted to have an elevated prolactin level as well as an elevated testosterone level. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. His last study visit was on day 121 and though his testosterone had returned to normal, his prolactin level was still elevated.

7.1.3.2.6 Discontinuations from TL023

Subject 12065/2312129
Adverse event: agitation, sweating increased
A 23 year old woman was receiving placebo. On Day 1, she was noted to have agitation and diaphoresis. She was discontinued on Day 2. This was unrelated to ramelteon.

7.1.3.2.7 Reviewer's summary

The adverse events that were seen were the ones, in general, that would have been expected in the development plan for a sedative-hypnotic. The only adverse events that were unusual were the endocrine findings. The potential endocrine effects were evaluated and are discussed in more detail later in this review.

7.1.3.3 Other significant adverse events

There were no other significant adverse events appropriate for discussion in this section.

7.1.4 Other Search Strategies

[*Reviewer's note: I performed searches based on apparent trends in the adverse event profile as well as the review by Huether (1993) which discussed extrapineal sites of melatonin synthesis, e.g. retina, gut(where it may act to decrease motility).*]

7.1.4.1 Abdominal pain

I performed a search of the adverse events database supplied with the 120-day safety update to assess what appeared to be an elevated incidence of complaints of abdominal pain in the study population.

I used the SOC term "Gastrointestinal disorders" to select the patients with abdominal pain. I then grouped all patients who had one or more of the following AEPN listed as an adverse event: Abdominal pain upper, abdominal discomfort, Abdominal pain NOS, Abdominal pain lower.

In the placebo group, 1.5% (n=20) of the patients had abdominal pain of some sort during Phase I-III studies. In the "all ramelteon group," 2.1% (n=74) patients had abdominal pain of some sort during Phase I-III studies. This finding will be described in the adverse events section of the label though because of the heterogeneity of the group, it will not appear in the adverse event listing.

7.1.4.2 Liver function tests

I performed a search of the adverse events database supplied with the 120-day safety update to assess what appeared to be an elevated incidence of liver function test (LFT) abnormalities in the study population.

I used the SOC term "investigations" to select the patients with abnormal LFTs. I then grouped all patients who had one or more of the following AEPN listed as an adverse event: Liver function tests abnormal, ALT increased/decreased, AST increased/decreased, Gamma-glutamyltransferase increased/decreased, total bilirubin increased/decreased, alkaline phosphatase increased/decreased.

There were 89 patients who met the stated criteria: 21 in the placebo group; 5 in the ramelteon 4 mg group; 20 in the ramelteon 8 mg group; 38 in the ramelteon 16 mg group. If a given patient had multiple AE on a given day, they were all bundled as one event in the table below and credited to the stated day. However, if a patient had AE reported on different days, each separate day was noted in the table below.

In order to decrease possible confounding from the use of study medications in drug-interaction studies, I only included patients who received either placebo or ramelteon. To further decrease possible confusion I removed those patients who had been enrolled on crossover studies. The numbers in the table below therefore represent a conservative reckoning of the true incidence.

In the placebo group, 1.5% (n=21) of the patients had abnormal liver function tests of some sort during Phase I-III studies. In the "all ramelteon group," 2.3% (n=84) patients had abnormal liver function tests of some sort during Phase I-III studies. This finding will be described in the adverse events section of the label though because of the heterogeneity of the group, it will not appear in the adverse event listing.

Table 26: Description of patients with abnormal liver function tests

		Day on study at onset of AE				
	Gender	**Days 1-7**	**Days 8-30**	**Days 31-60**	**Days 61-90**	**Days 91+**
Placebo	Males=12 Females=9	7	9	4	1	0
All ramelteon	Males=48 Females=36	26	29	19	5	0
Ramelteon 4mg	Males=2 Females=3	3	0	2	1	0
Ramelteon 8mg	Males=12 Females=8	10	6*	6*	0	2
Ramelteon 16mg	Males=21 Females=16	5	13	7	3	13*
Ramelteon 32mg	Males=1 Females=0	1	1*	0	0	0

(Data derived from the adverse events database submitted to the 120-day safety update)

7.1.4.3 Eye disorders

I performed a search of the adverse events database supplied with the 120-day safety update to assess what appeared to be an elevated incidence of eye disorders in the study population. In order to decrease possible confounding from the use of study medications in drug-interaction studies, I only included patients who received either placebo or ramelteon. To further decrease possible confusion I removed those patients who had been enrolled on crossover studies. The numbers in the table below therefore represent a conservative reckoning of the true incidence.

I divided the eye disorder complaints into two categories:

- physical complaints, which encompassed verbatim terms such as sore eyes, conjunctival irritation, dry eyes, watery eyes, etc.
- functional complaints, which encompassed photophobia, difficulty focusing , blurred vision, slowed eye movement, etc.

Table 27: Description of patients with eye disorders

	Males	Females	Physical	Functional
Placebo	10	20	17	10
Ramelteon 4 mg	9	20	17	11
Ramelteon 8 mg	16	24	31	16
Ramelteon 16 mg	9	28	31	13

In the placebo group, the majority of the complaints were physical. Of the complaints received, most were late effects occurring 8 to 70 days post first dose of study drug.

In the ramelteon 4 mg group, the majority of the complaints were physical. Of the complaints received, most were late effects occurring 8 to 43 days post first dose of study drug.

In the ramelteon 8 mg group, the majority of the complaints were physical. Of the complaints received, most were late effects occurring 8 to 43 days post first dose of study drug.

In the ramelteon 16 mg group, the majority of the complaints were physical. Of the complaints received, most were late effects occurring 8 to 227 days post first dose of study drug.

Overall, there did not appear to be a dose response relationship in the incidence of complaints: 2.2% of the placebo patients had eye disorder complaints as compared to 5.7% of the ramelteon 4 mg group, 3.2% of the ramelteon 8 mg group and 1.9% of the ramelteon 16 mg group. Overall 3% of the ramelteon patients complained of an eye disorder, usually as a late effect after 7 days of ramelteon use. This finding will be described in the adverse events section of the label though because of the heterogeneity of the group, it will not appear in the adverse event listing.

7.1.4.4 Endocrine

The sponsor performed special studies to evaluate the effect of ramelteon on endocrine function, those results may be found later in this review.

7.1.4.5 Next day residual effects

Since ramelteon is proposed for use as a hypnotic, studies of next day residual effects were performed, those results may be found in section 7.1.13.

7.1.4.6 Rebound after drug withdrawal

Since ramelteon is proposed for use as a hypnotic, studies of rebound after drug withdrawal were performed, those results may be found in section 7.1.13.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Phase I trials
During the Phase I single dose trials, subjects were assessed at screening and during the course of the trial for adverse events (AE).

Phase II/III trials
Spontaneously reported or investigator observed adverse events were recorded for participants at the initial screening and at all subsequent study visits. Only those symptoms whose onset occurred, severity worsened or intensity increased during the treatment period were to be reported as an adverse event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Treatment emergent adverse events (TEAE) were defined as events which occurred or worsened during study treatment, defined as the time between start of drug administration and within 7 days of the termination of dosing. Events which were present at baseline and increased in intensity or frequency were also considered TEAE.

The start of drug administration for double-blind studies was defined as the start of double-blind dosing, excluding the placebo run-in period. The termination of drug administration for double-blind studies was defined as the end of double-blind dosing, excluding the placebo run-out period.

Adverse events which occurred during crossover studies were counted in the treatment period of AE onset. AE which occurred during one treatment period, resolved then reoccurred during a subsequent treatment period were reported in both periods. AE which started in one treatment period and carried into a subsequent period without an interval of resolution were only counted in the period of onset.

Post treatment adverse events were those which occurred more than 7 days after the last dose of study drug. In all double-blind studies, the last dose of study drug is defined as the last dose in the double-blind period.

The time to AE onset was calculated as the start day of the event minus the date of the first day on drug plus 1. Duration of the AE was calculated as the stop date of the AE minus the start date of the AE plus 1 for each MedDRA preferred term.

If the date of the first dose of study medication were to be absent, the AE was considered treatment-emergent. For those AE which occurred in crossover studies, the AE was assigned to the treatment that preceded the AE onset. Any adverse events with missing stop dates were considered ongoing.

Adverse events were coded using MedDRA Dictionary version 5.0. The sponsor created "cluster terms" to attempt to evaluate the incidence of similar adverse events that may have been coded differently by individual investigators, as may be seen in the table below. The sponsor used the following rules in order to attempt to ensure consistency in the coding of adverse events relating to fatigue, somnolence and sedation (reproduced from p. 48-49 of the IAS):

- Any adverse event with "tired" in the verbatim term was coded to fatigue
- The exception to this was if the terms "groggy" or "sleepy" were also included in the verbatim term. If this occurred, the assigned code was somnolence
- Any adverse event with sedation in the verbatim term was coded to sedation

Table 28: Sponsor's cluster terms for adverse events

Cluster Term	MedDRA Preferred Terms
Anxiety	Anxiety, restlessness, stress symptoms, tension
Confusion	Amnesia, confusion, disorientation, disturbance in attention, judgment impaired, memory impairment
Depression	Crying, depression, depression aggravated, depressed mood, tearful
Disturbance in thinking and perception	Delirium, derealization, feeling abnormal, hallucination NOS, hypnagogic hallucination, thinking abnormal
Dizziness	Dizziness, dizziness aggravated, dizziness postural, vertigo, vertigo positional
Dyspepsia	Dyspepsia, dyspepsia aggravated, epigastric discomfort, hyperacidity
Fatigue	Fatigue, fatigue aggravated, lethargy, malaise, sluggishness, weakness
Muscle twitching	Muscle contractions involuntary, muscle twitching
Sensitivity increased	Burning sensation NOS, dysgeusia, hyperacusis, hyperesthesia, paresthesia, parosmia, photophobia, photosensitivity reaction NOS
Somnolence	Somnolence, sedation

This is a reproduction of table 6a. Source: Table 22.4.2.1.10, of the IAS.

7.1.5.3 Incidence of common adverse events

7.1.5.3.1 Incidence in Phase I to Phase III studies

The adverse events reported with the highest incidence during the Phase I-III trials were headache (8.3% in those who received ramelteon), somnolence (7.6% in those who received ramelteon), fatigue (4.1% in those who received ramelteon), dizziness (3.7% in those who received ramelteon), and nausea (3.1% in those who received ramelteon). When an analysis by the aforementioned cluster terms was done, the 8 mg group was noted to have a higher proportion of patients reporting depression and alteration in thinking/perception, adverse events associated with the sedative-hypnotics.

Table 29: Overall incidence by sponsor-defined cluster term

Cluster Term	Placebo (n=1370)	<4 mg (n=20)	Ramelteon 4 mg (n=511)	Ramelteon 8 mg (n=1250)	Ramelteon 16 mg (n=1961)	All Doses of Ramelteon (n=3594)
Anxiety	3 (0.2%)	0	4 (0.8%)	11 (0.9%)	20 (1.0%)	35 (1.0%)
Confusion	5 (0.4%)	0	6 (1.2%)	15 (1.2%)	13 (0.7%)	37 (1.0%)
Depression	11(0.8%)	0	11 (2.2%)	21 (1.7%)	15 (0.8%)	48 (1.3%)
Disturbance in thinking and perception	6 (0.4%)	0	7 (1.4%)	14 (1.1%)	3 (0.2%)	23 (0.6%)
Dizziness	49(3.6%)	1 (5.0%)	22 (4.3%)	56 (4.5%)	61 (3.1%)	141 (3.9%)
Dyspepsia	8 (0.6%)	0	4 (0.8%)	12 (1.0%)	20 (1.0%)	40 (1.1%)
Fatigue	33(2.4%)	6 (30.0%)	13 (2.5%)	60 (4.8%)	101(5.2%)	190 (5.3%)
Muscle twitching	5 (0.4%)	0	8 (1.6%)	11 (0.9%)	4 (0.2%)	23 (0.6%)
Sensitivity increased	39(2.8%)	0	19 (3.7%)	47 (3.8%)	20 (1.0%)	86 (2.4%)
Somnolence	47(3.4%)	8 (40.0%)	16 (3.1%)	64 (5.1%)	189(9.6%)	285 (7.9%)

Cluster Term	Placebo (n=1370)	Ramelteon 32 mg (n=169)	Ramelteon 64 mg (n=209)	All Doses of Ramelteon (n=3594)
Anxiety	3 (0.2%)	0	0	35 (1.0%)
Confusion	5 (0.4%)	1 (0.6%)	2 (1.0%)	37 (1.0%)
Depression	11 (0.8%)	0	1 (0.5%)	48 (1.3%)
Disturbance in thinking and perception	6 (0.4%)	0	0	23 (0.6%)
Dizziness	49 (3.6%)	0	2 (1.0%)	141 (3.9%)
Dyspepsia	8 (0.6%)	4 (2.4%)	0	40 (1.1%)
Fatigue	33 (2.4%)	2 (1.2%)	11 (5.3%)	190 (5.3%)
Muscle twitching	5 (0.4%)	0	0	23 (0.6%)
Sensitivity increased	39 (2.8%)	0	1 (0.5%)	86 (2.4%)
Somnolence	47 (3.4%)	5 (3.0%)	17 (8.1%)	285 (7.9%)

Table 6 d from the IAS, Source: Table 22.4.2.1.11.

In a subgroup analysis by age and cluster group, a higher proportion of adults who received ramelteon reported adverse events than then those who did not receive ramelteon: anxiety cluster (0.9% vs. 0.2%); confusion cluster (0.8% vs. 0.2%); dyspepsia cluster (1.1% vs. 0.3%); fatigue cluster (5.6% vs. 2.0%); somnolence cluster (8.4% vs. 3.2%). A higher proportion of elderly who received ramelteon reported adverse events than then those who did not receive ramelteon: anxiety cluster (1.2% vs. 0.3%); confusion cluster (1.6% vs. 0.8%); fatigue cluster (4.4% vs. 3.3%); somnolence cluster (6.5% vs. 4.1%).

In a subgroup analysis by gender and cluster group, in general a higher proportion of males who received ramelteon reported adverse events than females: anxiety cluster (0.9% vs. 1.1%); confusion cluster (1.4% vs. 0.8%); dyspepsia cluster (1.6% vs. 0.7%); fatigue cluster (5.9% vs. 4.9%); somnolence cluster (9.6% vs. 6.7%).

Though a subgroup analysis by ethnicity was done, the results are difficult to interpret due to the paucity of non-Caucasian patients.

7.1.5.3.2 Incidence in drug-interaction studies

The ramelteon doses used for these studies were 16 and 32 milligrams. Fatigue (19.9%), somnolence (12.1%), headache (7.4%), dizziness (5.1%), and nausea (3.0%) were the most frequently reported adverse effects in the patients who received ramelteon.

7.1.5.3.3 Incidence in Japanese studies

Somnolence (67.7%), impaired balance (11.3%), abnormal EEG (6.5%), dizziness (5.1%), pharyngitis (3.2%), nasophayngitis (2.4%) and nausea (3.0%) were the most frequently reported adverse effects in the patients who received ramelteon and all occurred at a higher proportion in those patients than in placebo. Headache NOS (6.5%), sedation (6.5%) and dizziness (3.2%) were all seen in both groups but at a higher proportion in the placebo group.

An independent expert reviewer found that the reported EEG abnormalities actually represented normal variants.

7.1.5.4 Common adverse event tables

[Reviewer's note: I have omitted the column for patients receiving less than 4 mg of ramelteon, though the data from those patients is included in the "all ramelteon" column.]

Table 30: Adverse events during Phase I-III studies (from IAS Table 6c and 120-day update)

		Ramelteon					
MedDRA Preferred Term	**Placebo (n=1370)**	**4 mg (n=511)**	**8 mg (n=1250)**	**16 mg (n=1961)**	**32 mg (n=169)**	**64 mg (n=209)**	**All**
Any adverse event	558 (40.7%)	191(37.4%)	596(47.4%)	928(47.3%)	56(33.1%)	74(35.4%)	1728(48.1%)
Headache NOS	92 (6.7%)	22 (4.3%)	88 (7%)	201(10.2%)	10(5.9%)	15 (7.2%)	299 (8.3%)
Somnolence	45 (3.3%)	13 (2.5%)	58 (4.6%)	204 (10.4%)	4(2.4%)	17(8.1%)	273 (7.6%)
Fatigue	26 (1.9%)	6 (1.2%)	44 (3.5%)	94 (4.8%)	2(1.2%)	10(4.8%)	148 (4.1%)
Dizziness	44 (3.2%)	20 (3.9%)	56 (4.5%)	66 (3.4%)	0	2(1.0%)	133 (3.7%)
Nausea	31 (2.3%)	11 (2.2%)	39 (3.1%)	78 (4.0%)	2(1.2%)	4(1.9%)	110 (3.1%)
Nasopharyngitis	35 (2.6%)	8 (1.6%)	34 (2.7%)	95 (4.8%)	1(0.6%)	1(0.5%)	86 (2.4%)
Insomnia exacerbated	23 (1.7%)	7 (1.4%)	38 (3.0%)	41 (2.1%)	0	0	74 (2.1%)
Upper respiratory tract infection NOS	26 (1.9%)	4 (0.8%)	33 (2.6%)	62(3.2%)	3(1.8%)	2(1.0%)	72 (2%)
Diarrhea NOS	24 (1.8%)	5 (1.0%)	24 (1.9%)	37(1.9%)	1(0.6%)	3(1.4%)	59 (1.6%)
Myalgia	12 (0.9%)	15 (2.9%)	21 (1.7%)	18(0.9%)	1(0.6%)	0	53 (1.5%)
Pharyngitis	16 (1.2%)	4 (0.8%)	16 (1.3%)	32(1.2%)	4(2.4%)	4(1.9%)	50 (1.4%)
Depression	8 (0.6%)	10 (2.0%)	20 (1.6%)	21 (1.1%)	0	1(0.5%)	44 (1.2%)
Dysgeusia	19 (1.4%)	8 (1.6%)	24 (1.9%)	6 (0.3%)	0	1(0.5%)	38 (1.1%)
Dry mouth	22 (1.6%)	7 (1.4%)	19(1.5%)	17 (0.9%)	0	2(1.0%)	39 (1.1%)
Back pain	12 (0.9%)	4 (0.8%)	19 (1.5%)	28 (1.4%)	1(0.6%)	0	38 (1.1%)
Dyspepsia	7 (0.5%)	4 (0.8%)	16 (1.3%)	24 (1.2%)	4(2.4%)	0	39 (1.1%)
Constipation	14 (1.0%)	4 (0.8%)	12(1.0%)	18 (0.9%)	9(5.3%)	7(3.3%)	36 (1.0%)
Pruritus NOS	20 (1.5%)	8 (1.6%)	10 (0.8%)	4 (0.2%)	8(4.7%)	7(3.3%)	36 (1.0%)
Sinusitis NOS	5 (0.4%)	6 (1.2%)	5 (0.4%)	40 (2.0%)	0	0	51 (1.4%)
Arthralgia	9 (0.7)	4 (0.8%)	19 (1.5%)	25 (1.3%)	0	0	48 (1.3%)
Nasal congestion	9 (0.7%)	5 (1%)	5 (0.4%)	25 (1.3%)	1(0.6%0	2 (1.0%)	39 (1.1%)
Influenza	2 (0.1%)	3 (0.6%)	9 (0.7%)	26 (1.3%)	0	0	38 (1.1%)
Blood Cortisol Decreased	2 (0.1%)	0	8 (0.6%)	29 (1.5%)	0	0	37 (1.0%)
Cough	9 (0.7%)	2 (0.4%)	8 (0.6%)	23 (1.2%)	2 (1.2%)	0	35 (1.0%)
Urinary tract infection NOS	17 (1.2%)	4 (0.8%)	14(1.1%)	23 (1.2%)	1(0.6%)	1(0.5%)	35 (1.0%)

7.1.5.5 Identifying common and drug-related adverse events

The following adverse events showed a consistent difference from control at the proposed marketed dose of 8 mg:

- Headache NOS

- Somnolence
- Fatigue
- Dizziness
- Nausea
- Nasopharnyngitis
- Insomnia exacerbated
- Upper respiratory tract infection NOS
- Myalgia
- Depression
- Dysgeusia
- Back pain
- Dyspepsia
- Arthralgia
- Influenza
- Blood cortisol decreased
- Eye disorders, including dry eyes, itchy eyes, photophobia

7.1.5.6 Additional analyses and explorations

There were no additional analyses or explorations of adverse events other than those which have been previously described.

7.1.6 Less Common Adverse Events

Prolactinoma
A 29 year old G_0P_0, with a past medical history notable only for myopia and insomnia both of which began in [ ] began treatment with 16 milligrams of TAK-375 daily on 7 August 2003 (Study TL-375-022). On [ ], prior to starting study medication, a serum beta HCG was performed and was found to be negative.

Her usual medications included ortho tri-cyclin (dates of use: [ ]), a daily multivitamin, and ibuprofen as needed for headaches. Her usual menstrual cycle was menses every 28 days with 5 days of slight bleeding.

She was noted to have cessation of menses, headaches and mild hair loss in [ ]

She had a laboratory evaluation on [ ] which was within normal limits for glucose, testosterone, FSH, LH and TSH but had two values which were outside the range of normal: DHEA 982 (130-980 ng/dl), prolactin 114.4 (normal range is 2.8-29.2 ng/ml). Study medication was stopped on March 22 2004, study day 228, due to the elevated prolactin level. She had a negative serum beta HCG test on [ ]

On [ ] she had a MRI scan of her head. This study was notable for an asymmetric pituitary gland. The right side of the gland, which was slightly larger than the left, contained an

ovoid focus (0.6 cm x 0.8 cm x 0.7 cm) of diminished signal that did not enhance with contrast. There were no other notable findings. The abnormal finding was consistent with a pituitary adenoma.

On [ ], she had her annual gynecological examination. At that time she complained of mild hair loss, headaches and hirsutism. She denied sexual activity. On examination she was found to have hirsutism of the chin, neck and lower abdomen. The examiner was able to express milk from both breasts. Her pelvic examination was normal. She was given an estrogen and progesterone challenge with 1.25 mg Menest for days 1-21 and Prometrium 400 mg days 11-21.

On [ ], she began bromocriptine therapy at a dose of 1.25 mg/daily initially. This dose was doubled after an unspecified amount of time.

She was seen for a follow-up visit on [ ] She had had a menstrual period on [ ] At that visit she was started on combination therapy with bromocriptine and Yasmin, an oral contraceptive, to address her hirsutism and galactorrhea. Her follow-up laboratory results from [ ] prolactin 106.6 (normal range is 2.8-29.2 ng/ml); DHEA 354, progesterone 68 (follicular 15-70 ng/dl, luteal 35-290 ng/dl).

Her follow-up prolactin level was 27.7 on [ ]. As of [ ] the prolactinoma was being managed via medical means, no surgical intervention had been performed.

Her adverse event profile also includes headache in [ ] as well as swollen right knee and medial joint tendonitis from [ ]

Reviewer's note:
Prolactinomas are the most common of the pituitary gland tumors, representing 30-40% of the tumors seen in clinical practice. Prolactinomas account for 15% of all primary intracranial tumors that come to surgical attention. Women, who represent 78% of the prolactinoma patients seen, usually present in the 2nd or 3rd decade of life complaining of amenorrhea and/or galactorrhea. Men more commonly present in the 4th or 5th decade of life with complaints of decreased libido, erectile dysfunction, headache and visual loss. The differences in the presentation may lead to an ascertainment bias. Some people may have a genetic predisposition to prolactinoma, but not actually develop a tumor until exposed to an external agent. There is no way of ascertaining in which persons a genetic predisposition may exist.

As we realize that this product may increase prolactin levels in some users, we must try to assess the clinical significance of this change in hormone secretion. The major adverse effect of concern would be hypogonadism related to chronic hyperprolactinemia and resultant decrease in libido, alterations in fertility and osteopenia. In females, with hyerprolactinemia in the absence of a mass lesion, the sentinel findings would be amenorrhea followed by galactorrhea. The concerned clinician could discontinue the ramelteon while awaiting results of a prolactin level. If the prolactin level were found to be high, the medication could be permanently discontinued and the patient would be expected to return to baseline prolactin level upon drug withdrawal. In males the sentinel finding include decreased libido and infertility. However, these

changes may be gradual and may not be readily apparent. While the finding would respond to drug withdrawal, the clinician would have to realize that this would be the appropriate intervention instead of perhaps prescribing a medication for erectile dysfunction.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

All of the placebo-controlled chronic insomnia studies collected laboratory data:

- TL005: Blood sampling was done at baseline and at the final visit. The sponsor assigned the values to the last treatment received in this 5-period crossover study.
- TL017: Blood sampling was done at baseline, at the end of the second period and at the final visit. The sponsor assigned the values to the treatments received in the last two periods of this 3-period crossover study.
- TL020, TL021, TL025: Laboratory values were obtained at baseline, week 2 and the end of treatment.

The following healthy volunteer studies collected laboratory data: PNFP 02, TL023, PNFP001, TL003, TL031, EC002, TL006 and TL040, all of which were placebo controlled studies; TL004, EC003 and EC004, all of which were done without a comparator. The sponsor elected not to integrate the laboratory data from study EC004 since that data was obtained one week post-dose. Endocrine parameters were evaluated in a select group of studies. Those results will be further discussed in section 7.1.12. I will limit the analysis of the laboratory findings to the chronic insomnia studies, and simply summarize the findings form the healthy volunteer studies, which have the possible confounding factor of multiple blood draws.

Table 31: Laboratory variables assessed during clinical studies

Hematology		**Serum Chemistry**	
Hematocrit		Electrolytes:	Liver function:
Hemoglobin		Sodium	ALT
RBC		Potassium	AST
Platelet count		Chloride	GGT
WBC		Bicarbonate	Bilirubin—total
	Basophils: % and absolute value	CO_2	Bilirubin—direct
	Eosinophils: % and absolute value	Calcium	Alkaline phosphatase
	Lymphocytes: % and absolute value	Magnesium	
	Monocytes: % and absolute value	Phosphate- phosphorus	
	Neutrophils: % and absolute value		
Metabolic Function		**Renal Function**	**Urinalysis**
Cholesterol-total	Albumin	BUN	pH
Triglycerides	Total protein	Creatinine	Specific gravity
Glucose	Uric acid		
LDH			

(Table 7a from the IAS)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The data from the placebo-controlled chronic insomnia studies was pooled by the sponsor. The data from the studies done in healthy volunteers was also pooled by the sponsor, though it was presented separately from the data from the placebo-controlled chronic insomnia studies.

Baseline for clinical laboratory evaluations was defined as the measurements obtained prior to the first dose of study medication of any sort. However, measurements taken on Day 1 of the study were considered to have been taken prior to the subject's first dose since the measurements were taken during the day and the first dose of the medication was to be dosed that night.

Laboratory measurements taken from within 3 days of study drug termination were considered on-treatment values. Endpoint values were the last values obtained on treatment. The last available measurements were used in all cases, even when participants did not complete the study.

Reference ranges from the central laboratory, in those studies which used the services of a central laboratory, were used to create the shift tables. In those studies that did not use a central laboratory, the local laboratory reference ranges were used. Gender specific reference ranges were used whenever applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology

Overall, there were no significant changes from baseline seen in the values from the chronic insomnia population, as may be seen in table below.

In the healthy volunteers, a small mean decrease in white blood cells, hemoglobin, platelets and red blood cells was seen. This may reasonably be attributed to the multiple blood samples associated with pharmacokinetic sampling.

Table 32: Shift table for the chronic insomnia studies

		Ramelteon			
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**
Hemoglobin (g/L)					
n	737	341	729	420	20
Baseline (±SD)	140.4±13.58	140.5±12.92	139.8±13.75	140.2±13.81	136.6±13.43
Change from Baseline (mean±SE)	-0.5±0.25	-0.4±0.37	-0.2±0.25	1.0±0.34	-0.8±1.29
RBC ($x10_{12}$/L)					
n	737	341	729	420	20
Baseline (±SD)	4.68±0.443	4.64±0.437	4.68±0.457	4.68±0.474	4.55±0.369
Change from Baseline (mean±SE)	-0.01±0.009	-0.00±0.012	0.01±0.009	0.05±0.012	-0.05±0.044

Table 32: Shift table for the chronic insomnia studies (continued)

Platelets (x10⁹/L)					
n	734	340	721	420	20
Baseline (±SD)	268.4±68.75	259.5±66.90	266.3±67.17	273.0±69.72	257.2±42.00
Change from Baseline (mean±SE)	-2.1±1.51	2.4±2.26	-2.6±1.38	-5.7±1.89	10.4±9.53
WBC (x10⁹/L)					
n	737	341	729	420	20
Baseline (±SD)	7.12±1.995	6.79±1.809	7.02±2.083	7.08±2.001	5.28±1.353
Change from Baseline (mean±SE)	-0.423±0.061	-0.027±0.078	-0.256±0.054	-0.372±0.088	0.095±0.225
Neutrophils (%)					
n	737	341	729	420	20
Baseline (±SD)	59.2±9.00	60.8±8.78	59.5±8.63	58.4±8.59	59.7±7.48
Change from Baseline (mean±SE)	-0.95±0.29	-0.51±0.40	-0.73±0.26	-1.66±0.38	-2.95±2.42
Lymphocytes (%)					
n	737	341	729	420	20
Baseline (±SD)	31.7±8.49	30.0±8.32	31.5±8.40	33.0±7.95	31.4±7.22
Change from Baseline (mean±SE)	0.82±0.30	0.47±0.35	0.64±0.24	1.47±0.34	2.37±2.14

(This is a modification of table 7b from the IAS. The data has been cross-referenced with Table 22.5.1.1.1 from the IAS.)

Chemistry

Overall, there were no significant changes from baseline seen in the values from the chronic insomnia population, as may be seen in table below. Overall, there were no significant changes from baseline seen in the chemistry values from the healthy volunteer population.

Table 33: Shift table for the chronic insomnia studies

		Ramelteon			
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**
ALT (U/L)					
n	741	345	731	423	20
Baseline (±SD)	21.5±11.93	20.3±10.30	21.6±13.44	21.2±11.79	19.1±8.33
Change from Baseline (mean±SE)	-0.0±0.34	-1.1±0.38	-0.6±0.52	-0.3±0.44	2.6±2.58
AST (U/L)					
n	738	344	731	422	20
Baseline (±SD)	22.7±7.02	23.2±7.59	22.8±7.76	21.4±6.71	22.0±6.57
Change from Baseline (mean±SE)	-0.0±0.27	-0.9±0.31	-0.7±0.29	-0.4±0.29	0.4±0.97
GGT (U/L)					
n	743	345	732	423	20
Baseline (±SD)	25.5±19.71	27.2±24.77	25.6±21.35	25.4±21.01	21.6±12.19
Change from Baseline (mean±SE)	-0.2±0.45	-1.0±1.24	-0.6±0.47	-1.0±0.43	0.4±2.49
Total bilirubin (µmol/L)					
n	742	346	731	423	20
Baseline (±SD)	8.9±5.02	9.6±4.43	8.6±4.33	8.4±5.01	8.9±4.08
Change from Baseline (mean±SE)	0.5±0.15	0.2±0.18	0.7±0.14	0.5±0.20	0.5±0.82

Table 33: Shift table for the chronic insomnia studies (continued)

Creatinine (µmol/L)					
n	743	346	732	423	20
Baseline (±SD)	74.2±19.03	77.5±23.23	75.7±19.17	71.2±14.32	73.4±20.11
Change from Baseline (mean±SE)	-0.3±0.41	1.4±0.55	-0.3±0.40	0.3±0.50	8.5±3.06
BUN (mmol/L)					
n	743	346	732	423	20
Baseline (±SD)	5.77±1.833	6.46±2.387	5.79±1.989	5.18±1.595	4.80±1.339
Change from Baseline (mean±SE)	-0.055±0.052	0.119±0.074	-0.026±0.050	-0.100±0.067	0.447±0.303
Albumin (g/L)					
n	742	346	731	423	20
Baseline (±SD)	42.5±2.98	42.1±3.03	42.6±3.15	43.1±3.10	42.2±2.81
Change from Baseline (mean±SE)	-0.5±0.09	-0.7±0.13	-0.5±0.10	-0.4±0.12	-0.9±0.42
Total protein (g/L)					
n	743	346	732	423	20
Baseline (±SD)	71.9±4.31	71.5±4.31	71.8±4.51	72.1±4.64	73.5±4.52
Change from Baseline (mean±SE)	-0.7±0.14	-0.9±0.19	-0.8±0.15	-0.7±0.17	-1.1±0.82

(This is a modification of table 7f from the IAS. The data has been cross-referenced with Table 22.5.1.1.2 from the IAS.)

Urinalysis

There were no significant changes from baseline in the pH or specific gravity seen in the chronic insomnia population or in the healthy volunteer population.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

[*Reviewer's note: In general, I have only reported those instances where the proportion of affected persons was higher in a ramelteon group than in the placebo group.*]

Hematology

Hematocrit

- On Day 3, 1% (4 mg group) to 3% (8-, 16- mg groups) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which none of the participants had such a change. A change from low/normal to high was only seen in the 4 mg group, in 1% of those participants.
- On Day 15, 1% (8-, 16- mg groups) to 3% (4 mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 1% of the participants had such a change. There is no data from the 32 mg group for this day.
- On Day 35, 1% (8-,16 mg groups) to 3% (4 mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 1% of the participants had such a change. There is no data from the 32 mg group for this day.

White blood cells

- On Day 3, 2% (4-, 8- mg group), 3% (16 mg group) and 15% (32 mg group, n=3) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 2% of the participants had such a change.
- On Day 15, 2% (4, 8 mg group) and 4% (16 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 3% of the participants had such a change. On the same day, 1% (4-, 8- mg group) and 2% (16 mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 1% of the participants had such a change. There is no data from the 32 mg group for this day.
- On Day 35, 1% (16 mg group), 2% (8 mg group) and 3% (4 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. There is no data from the 32 mg group for this day.

Platelets

- On Day 3, 1% (4, 8 mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 2% of the participants had such a change. On the same day, none of the subjects in any group had a change from a low/normal value to a high value.
- On Day 15, 1% (4 mg group) and 2% (8-, 16- mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, approximately 1% of all subjects in each of the four groups with available data had a change from a high/normal value to a low value. There is no data from the 32 mg group for this day.
- On Day 35, 2% (4-, 16- mg groups) and 2% (8 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 2% of the participants had such a change. On the same day, <1% (16 mg group only) of the subjects receiving ramelteon had a change from a high/normal value to a low value, identical to the placebo group. There is no data from the 32 mg group for this day.

In the healthy volunteers, a change from high/normal to low for white blood cells, hemoglobin, platelets and red blood cells was seen in some cases. While this may be partially attributed to the multiple blood samples associated with pharmacokinetic sampling, the differences from the placebo group cannot be accounted for by that explanation. However, it is difficult to fully assess due to the small numbers of patients involved in some of the dose groups.

Table 34: Shift table for healthy volunteers-Hematology

		Ramelteon					
	Placebo	**<4 mg**	**4 mg**	**8 mg**	**16 mg**	**32 mg**	**64 mg**
Hemoglobin (g/L)							
Day 3 n (%) L/N to H	2 (1%)	0	0	0	1 (<1%)	0	0
Day 3 n (%) H/N to L	12 (4%)	1 (6%)	0	1 (1%)	10 (3%)	5 (8%)	9 (5%)
Day 15 n (%) L/N to H	0	No data	No data	No data	0	0	0
Day 15 n (%) H/N to L	4 (6%)	No data	No data	No data	6 (7%)	3 (23%)	2 (15%)
Day 35 n (%) L/N to H	0	No data	No data	No data	0	No data	No data
Day 35 n (%) H/N to L	0	No data	No data	No data	1 (2%)	No data	No data
RBC (x10^{12}/L)							
Day 3 n (%) L/N to H	0	0	1 (8%)	0	0	0	1 (1%)
Day 3 n (%) H/N to L	8 (2%)	0	0	1 (1%)	12 (4%)	2 (3%)	5 (3%)
Day 15 n (%) L/N to H	0	No data	No data	No data	0	0	0
Day 15 n (%) H/N to L	4 (6%)	No data	No data	No data	7 (8%)	3 (23%)	9 (30%)
Day 35 n (%) L/N to H	0	No data	No data	No data	0	No data	No data
Day 35 n (%) H/N to L	3 (7%)	No data	No data	No data	1 (2%)	No data	No data
Platelets (x10^{9}/L)							
Day 3 n (%) L/N to H	0	1 (6%)	0	1 (1%)	1 (<1%)	0	1 (1%)
Day 3 n (%) H/N to L	1 (<1%)	0	1 (8%)	1 (1%)	0	0	2 (1%)
Day 15 n (%) L/N to H	0	No data	No data	No data	1 (1%)	0	0
Day 15 n (%) H/N to L	0	No data	No data	No data	4 (4%)	0	0
Day 35 n (%) L/N to H	0	No data	No data	No data	1 (2%)	No data	No data
Day 35 n (%) H/N to L	0	No data	No data	No data	0	No data	No data
WBC (x10^{9}/L)							
Day 3 n (%) L/N to H	3 (1%)	0	0	1 (1%)	1 (<1%)	0	0
Day 3 n (%) H/N to L	13 (4%)	0	0	2 (2%)	8 (3%)	1(2%)	2(1%)
Day 15 n (%) L/N to H	0	No data	No data	No data	0	0	0
Day 15 n (%) H/N to L	1 (1%)	No data	No data	No data	1 (1%)	0	0
Day 35 n (%) L/N to H	0	No data	No data	No data	1 (2%)	No data	No data
Day 35 n (%) H/N to L	0	No data	No data	No data	0	No data	No data

(This is a modification of Table 7m from the IAS)

Chemistry

AST

- On Day 3, 6% (4 mg group) and 3% (8 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 4% of the participants had such a change. On the same day, approximately 1% of the subjects in the 8 mg group had a change from a high/normal value to a low value.
- On Day 35, 1% (4 mg group), 2% (8 mg group) and 3% (16 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 2% of the participants had such a change. On the same day, <1% (3-, 16- mg groups) of the subjects receiving ramelteon had a change from a

high/normal value to a low value, as compared to none in the placebo group. There is no data from the 32 mg group for this day.

Total bilirubin

- On Day 3, 1% (16 mg group) and 4% (4 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 3% of the participants had such a change. On the same day, 1 participant in the placebo group (1%) and 1 in the 16 mg group (3%) had a change from a high/normal value to a low value.
- On Day 15, 2% (4 mg group) and 1% (8-, 16- mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, <1% (4 mg group), 4% (8 mg group) and 5% (16 mg group)of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 3% of the participants had such a change. There is no data from the 32 mg group for this day.
- On Day 35, 3% (4 mg group) and 2% (8-, 16-mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, 1% (4 mg group) and 2% (8-, 16-mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, as compared to the placebo group in which 1% of the participants had such a change. There is no data from the 32 mg group for this day.

BUN

- On Day 3, 1% (4- , 8- mg group) and 2% (8 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, none of the subjects in any group had a change from a high/normal value to a low value.
- On Day 15, 3% (4 mg group), 2% (8 mg group) and 1% (16 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 2% of the participants had such a change. On the same day, none of the subjects in any group had a change from a high/normal value to a low value. There is no data from the 32 mg group for this day.
- On Day 35, 3% (4 mg group), 1% (8 mg group) and 2% (16 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 2% of the participants had such a change. On the same day, none of the subjects in any group had a change from a high/normal value to a low value. There is no data from the 32 mg group for this day.

Albumin

- On Day 3, 1% (4- , 8- mg group) of the subjects receiving ramelteon had a change from a high/normal value to a low value, identical to the placebo group in which 1% of the participants had such a change. On the same day, none of the subjects in any group had a change from a high/normal value to a low value.
- On Day 15, 1% (4- ,16- mg group), and 2% (8 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, less

than 1% of the subjects in the 8 mg group had a change from a high/normal value to a low value. No such change was seen in the 4 mg, 16 mg or placebo group. There is no data from the 32 mg group for this day.

- On Day 35, 2% (4-, 8- mg group), and 1% (16 mg group) of the subjects receiving ramelteon had a change from a low/normal value to a high value, as compared to the placebo group in which 1% of the participants had such a change. On the same day, less than 1% of the subjects in the 8 mg group had a change from a high/normal value to a low value. No such change was seen in the 4 mg, 16 mg or placebo group. There is no data from the 32 mg group for this day.

Overall the healthy volunteer population did not evidence clinically significant shifts in chemistry values.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Hematology

Overall, less than 2% of the participants in the chronic insomnia trials had markedly abnormal hematology values:

- Hematocrit (≤37% M/≤32%F): 7 in the placebo group (0.8%), 11 in the 4 mg group (2.3%), 6 in the 8 mg group (0.7%) and 1 in the 16 mg group (0.2%).
- WBC: 1 in the placebo group (0.2%) and 1 in the 8 mg (0.2%) group
- Eosinophils (>10%): 2 each in the placebo (0.2%), the 8 mg (0.2%)and the 16 mg (0.2%) groups

Overall, less than 1% of the participants in the trials performed with healthy volunteers had markedly abnormal hematology values.

Chemistry

Overall, less than 2% of the participants in the chronic insomnia trials had markedly abnormal chemistry values:

- Calcium (≤8.2 mg/dL): 2 in the placebo group (0.2%) and 1 in the 8 mg (0.1%) group
- Potassium (≥5.8 mEq/L): 7 in the placebo group (0.8%), 5 in the 4 mg group (1%), 4 in the 8 mg group (0.4%) and 1 in the 16 mg group (0.2%)
- Chloride (≥115mEq/L): 1 in the placebo group (0.1%), 2 in the 8 mg group (0.2%) and 2 in the 16 mg group (0.4%)
- Phosphorus (≥6 mg/dl): 1 in the 8 mg (0.1%) group
- ALT ≥ 3 x upper limit of normal (ULN): 1 in the placebo group (0.1%), 2 in the 8 mg group (0.2%)
- AST ≥ 3 x (ULN): 3 in the placebo group (0.3%), 2 in the 8 mg group (0.2%) and 1 in the 16 mg group (0.2%)
- GGT ≥ 3 x (ULN): 1 in the 4 mg group (0.2%)
- Total bilirubin ≥2mg/dL: 1 in the placebo group (0.1%), 2 in the 8 mg group (0.2%)
- Glucose ≤ 50 mg/dL: 1 in the placebo group (0.1%), 1 in the 4 mg group (0.2%), 1 in the 8 mg group (0.2%) and 1 in the 16 mg group (0.2%)

- Glucose ≥180 mg/dL: 4 in the placebo group (0.4%), 5 in the 8 mg group (0.6%) and 2 in the 16 mg group (0.4%)
- BUN > 30 mg/dL: 5 in the placebo group (0.6%), 11 in the 4 mg group (2.3%), 9 in the 8 mg group (1%) and 2 in the 16 mg group (0.4%)
- Uric acid (M: ≥10.5, F: ≥8.5): 3 in the placebo group (0.3%), 3 in the 8 mg group (0.6%)

In the healthy volunteer studies, a few patients represented outliers.

- Subject 12093/231237 (Ramelteon 8 mg): Elevated ALT of 211 U/L, AST of 490 U/L and LDH of 726 U/L after a single doe of ramelteon. His baseline laboratory values were normal. By 2 days post-dosing, his values were beginning to normalize and by 8 days post-dosing, only the 48 remained above reference range at 48 U/L.
- Subject 12817/231156 (Placebo): Elevated total bilirubin of 2.7 mg/dL
- Subject 12041/1014 (Ramelteon 16 mg) had a potassium of 5.8 mEq/L on Day 2 which was noted to be 5.1 at the end of the study

Urinalysis

Overall, less than 2% of the participants in the chronic insomnia trials had markedly abnormal urinalysis values:

- pH >7: 18 in the placebo group (2%), 2 in the 4 mg group(0.4%), 11 in the 8 mg group (1.2%) and 15 in the 16 mg group (2.8%)
- Specific gravity < 1.005: 3 in the placebo group (0.3%), 4 in the 8 mg group (0.4%) and 1 in the 16 mg group (0.2%)

Overall, approximately 2% of the participants in the chronic insomnia trials had markedly abnormal urinalysis values:

- pH >7: 10 in the placebo group (2.5%), 1 in the <4 mg group (5%), 14 in the 16 mg group (3.4%) and 2 in the 16 mg group (1%)
- Specific gravity < 1.005: 4 in the 16 mg group (0.6%)

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations of the laboratory data were done during the review of this New Drug Application.

7.1.7.5 Special assessments

No special assessments of the laboratory data were done during the review of this New Drug Application. Attention was focused upon endocrine parameters as a result of concerns raised during the development program; a detailed discussion of the endocrine studies and their findings may be found in section 7.1.12 of this review.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

During the chronic insomnia studies, pulse measurements and sitting blood pressure measurements were obtained. In TL 005 and TL017, the two crossover studies, vital signs were obtained at baseline, before dosing and the following morning. In the other three studies, TL 020, TL021, and TL 025, vital signs were measured at each visit.

For most of the healthy volunteer studies, vital sign measurements consisted of 5–minute sitting blood pressure and pulse measurements. In studies EC002, EC003 and EC004, supine blood pressure and pulse were also obtained. In the healthy volunteer studies, vital sign measurements were obtained at each visit for the outpatient studies or each day for the inpatient studies. In PNFP 001, sitting blood pressure and pulse were obtained every 15 minutes for the first 2 hours, every 30 minutes for the next two hours and then at 6, 8, and 24 hours post dosing. In TL050 sitting blood pressure and pulse were obtained 3 and 6 hours post-dose. In EC003, supine blood pressure and pulse were obtained as 1.5, 4, 12 and 24 hours following the oral formulation and at 10 minutes, 1.5-, 4-, 12- and 24 hours following administration of the intravenous formulation. In EC004, supine measurements were obtained at 1.5, 8 and 168 hours post-dose.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The data from the placebo-controlled chronic insomnia studies was pooled by the sponsor. The data from the studies done in healthy volunteers was also pooled by the sponsor, though it was presented separately from the data from the placebo-controlled chronic insomnia studies.

The day of study was calculated as the actual date of the measurement minus the date of the first dose of study drug plus 1. In the case of the double-blind Phase II/III trials, the placebo run-in and run-out periods were excluded.

Baseline measurements were those measurements obtained prior to dosing, excluding placebo run-in and run-out periods. In those cases where more than one measurement was obtained during the baseline period, the last measurement prior to dosing was use for calculation of baseline.

Vital sign measurements taken from within 3 days of study drug termination were considered on-treatment values. Endpoint values were the last values obtained on treatment. The last available measurements were used in all cases, even when participants did not complete the study.

In crossover trials, only those measurements obtained within 3 days of a particular treatment period were analyzed. If measurements were made for more than one treatment period in a crossover study, the analysis was summarized in the appropriate treatment group. If measurements were made only at the end of the study, the measurements were attributed to the last treatment received.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

There were no clinically significant shifts in vital signs during the chronic insomnia studies.

Table 35: Shift table for vital signs in placebo-controlled chronic insomnia studies

		Ramelteon			
	Placebo	4 mg	8 mg	16 mg	32 mg
Systolic blood pressure (mmHg)					
n	878	479	877	518	105
Baseline (±SD)	123.2±15.42	127.7±15.40	123.8±15.51	118.2±13.65	117.2±11.83
Change from Baseline to Endpoint (mean±SE)	-1.9±0.45	-1.8±0.63	-2.8±0.44	-2.9±0.51	-3.7±1.07
Diastolic blood pressure (mmHg)					
n	878	479	877	518	105
Baseline (±SD)	75.1±9.30	74.9±8.77	75.4±8.90	75.5±8.78	76.7±8.81
Change from Baseline to Endpoint (mean±SE)	-0.6±0.31	-0.8±0.39	-1.1±0.29	-1.5±0.37	-1.8±0.97
Heart rate (beats per minute)					
n	880	479	877	517	105
Baseline (±SD)	71.7±9.57	71.7±10.18	71.7±9.52	73.0±10.01	74.8±10.03
Change from Baseline to Endpoint (mean±SE)	-2.1±0.34	-3.1±0.41	-2.4±0.32	-3.0±0.44	-2.7±1.00

Source: Tables 22.6.1.1, 22.6.1.2, 22.6.1.3, and 22.6.1.4.

Table 8a from the IAS

There were no clinically significant shifts in vital signs during the healthy volunteer studies.

Table 36: Shift table for vital signs in healthy volunteer studies

		Ramelteon					
	Placebo	<4 mg	4 mg	8 mg	16 mg	32 mg	64 mg
Systolic blood pressure (mmHg)							
n	369	9	25	106	366	63	208
Baseline (±SD)	117.0±12.0	115.0±12.36	126.5±10.85	117.5±11.52	117.3±12.55	111.3±10.39	115.3±11.56
Change (mean±SE)	-2.7±0.53	-0.2±3.93	-9.2±1.61	-5.3±1.02	-3.4±0.56	-2.0±1.16	-2.7±0.72
Diastolic blood pressure (mmHg)							
n	369	9	25	106	366	63	208
Baseline (±SD)	74.8±9.0	63.9±6.17	77.5±8.86	73.8±9.49	73.9±9.31	71.6±6.98	115.3±11.56
Change (mean±SE)	-1.4±0.44	-0.9±2.14	-3.0±1.11	-3.4±0.83	-2.4±0.45	0.3±0.82	-2.1±0.61
Heart rate (beats per minute)							
n	369	10	25	106	365	63	208
Baseline (±SD)	71.2±9.61	56.4±5.85	56.4±5.85	72.5±9.71	69.5±11.26	72.1±5.70	67.7±8.62
Change from Baseline to Endpoint (mean±SE)	-2.5±0.49	-0.6±1.29	-0.6±1.29	-5.4±0.98	-2.3±0.55	-0.6±0.78	0.7±0.60

Table 8d from the IAS, Source: Tables 22.6.2.1, 22.6.2.2, 22.6.2.3, and 22.6.2.4.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Upon review of the data from the chronic insomnia studies, while the proportions are small, there is noted to be a slight trend toward lowering of the systolic blood pressure in the ramelteon group. While it must be noted that the highest dose group had the incidence closest to that of placebo, the 32 mg group also had the smallest number of participants. These changes would appear to be dose related. I would also note that the proportion of patients with bradycardia appears to have a dose-related trend in this subset.

Table 37: Placebo-controlled chronic insomnia studies

		Ramelteon				
	Placebo	**4 mg**	**8 mg**	**16 mg**	**32 mg**	**All Doses**
Systolic blood pressure (mmHg)						
n	881	479	878	519	105	1565
≤90 and decrease ≥20	11 (1.2%)	3 (0.6%)	15 (1.7%)	13 (2.5%)	1 (1.0%)	31 (2.0%)
≥180 and increase ≥20	0	0	7 (0.8%)	0	0	7 (0.4%)
Diastolic blood pressure (mmHg)						
n	881	479	878	519	105	1565
≤50 and decrease ≥15	8 (0.9%)	1 (0.2%)	13 (1.5%)	8 (1.5%)	0	22 (1.4%)
≥105 and increase ≥15	7 (0.8%)	1 (0.2%)	1 (0.1%)	2 (0.4%)	0	4 (0.3%)
Heart rate (bpm)						
n	882	479	877	519	105	1564
≤50 and decrease ≥15	8 (0.9%)	5 (1.0%)	14 (1.6%)	10 (1.9%)	0	29 (1.9%)
≥120 and increase ≥15	1 (0.1%)	0	0	0	0	0

Table 8b from the IAS

Again, while the proportions are small, there is noted to be a slight trend toward dose related systolic changes in the ramelteon arm of the healthy volunteer studies. The results from the 32 milligram group may be confounded by the small sample size.

Table 38: Placebo-controlled healthy volunteer studies

		Ramelteon					
Placebo		**<4 mg**	**4 mg**	**8 mg**	**16 mg**	**32 mg**	**64 mg**
Systolic blood pressure (mmHg)							
n	385	20	25	106	382	64	209
≤90 and decrease ≥20	4 (1%)	0	0	2 (1.9%)	8 (2.1%)	1 (1.0%)	7 (3.3%)
≥180 and increase ≥20	1 (0.3%)	0	0	0	0	0	0
Diastolic blood pressure (mmHg)							
n	385	20	25	106	382	64	209
≤50 and decrease ≥15	2 (0.5%)	1 (5%)	0	1 (0.9%)	1 (0.3%)	0	2 (1.0%)
≥105 and increase ≥15	0	0	0	0	0	0	1 (0.5%)
Heart rate (bpm)							
n	385	20	25	106	381	64	209
≤50 and decrease ≥15	7 (1.8%)	0	0	1 (0.9%)	14 (3.7%)	0	1 (0.5%)

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations of the vital signs data were done during the review of this New Drug Application.

7.1.8.5 Special assessments

No special assessments of the vital signs data were done during the review of this New Drug Application.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiogram data was obtained in both the placebo-controlled chronic insomnia studies and in the healthy volunteer studies.

In study TL017, which was a 3-period crossover study, ECG readings were obtained after the second and third treatment sequences. For studies 020, 021 and 025, ECG readings were obtained during screening as well as at the end of the double-blind treatment period.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

In study TL005, no interval data was provided only an ECG interpretation, therefore the sponsor did not include information from this study in the analysis. Data from the other 4 placebo-controlled trials was included in the analysis.

Healthy volunteer studies EC004 and TL031 had post-dose measurements made 1 and 2 weeks after the last dose, respectively; the data from those two studies was not included in the analysis.

Healthy volunteer studies TL006 and EC002 had ECG interpretations without interval data; the data from those two studies was not included in the analysis.

All ECG acquisition, interpretation and analysis was performed by [redacted]

The day of study was calculated as the actual date of the measurement minus the date of the first dose of study drug plus 1. In the case of the double-blind Phase II/III trials, the placebo run-in and run-out periods were excluded.

Baseline measurements were those measurements obtained prior to dosing, excluding placebo run-in and run-out periods. In those cases where more than one measurement was obtained

during the baseline period, the last measurement prior to dosing was use for calculation of baseline.

ECG measurements taken from within 3 days of study drug termination were considered on-treatment values. The time intervals for study periods were Day 3 (days 2-7), day 15 (Days 8-21), Day 35 (Days 22 and greater) as long as measurements were obtained within 3 days of study treatment discontinuation. Endpoint values were the last values obtained on treatment. The last available measurements were used in all cases, even when participants did not complete the study.

In crossover trials, only those measurements obtained within 3 days of a particular treatment period were analyzed. If measurements were made for more than one treatment period in a crossover study, the analysis was summarized in the appropriate treatment group. If measurements were made only at the end of the study, the measurements were attributed to the last treatment received.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Chronic insomnia patients

A review of the descriptive statistics for heart rate, PR interval, QRS interval and QTc (fridericia) did not reveal any meaningful differences from placebo for the studied doses of ramelteon: 4 mg, 8 mg, 16 mg, 32 mg when the change from baseline to endpoint was evaluated.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Chronic insomnia patients

A higher proportion of increases from baseline in QTc of at least 30 msec was seen in the ramelteon group (6.3%) as compared to the placebo group (4.2%).

While overall the incidence of PR intervals > 220 msec was < 1% in both groups, the incidence of this finding in the 4 mg group was 1.3% as compared to the placebo group which had an incidence of 0.3%.

While overall the incidence of QRS intervals > 120 msec was < 1% in both groups, the incidence of this finding in the 4 mg group was 1.9% as compared to the placebo group which had an incidence of 0.6%.

Healthy volunteers

A higher proportion of increases from baseline in QTc of at least 30 msec was seen in the ramelteon group (6%) as compared to the placebo group (4%): 14.3% (n=1) in the <4 mg group, 5% in the 8 mg group, 5.8% in the 16 mg group, and 6.7% in the 64 mg group; there were no patients in the 4 mg or 32 mg groups. While this finding might cause one to hypothesize about a possible dose effect, the finding is not supported by the results from the moxifloxacin study described in section 7.1.9.4

While overall the incidence of PR intervals > 220 msec was < 1% in both groups, the incidence of this finding in the 8 mg group was 1.7% as compared to the placebo group which had an incidence of 0.6%.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Chronic insomnia

The only ECG changes reported as adverse events at a proportion higher than that of placebo were QT prolonged, QTc prolonged and ST-T change NOS; all were reported by 1 patient, giving a rate of 0.1-0.2%.

7.1.9.4 Additional analyses and explorations

TL 040 was a single-blind placebo controlled 4-period crossover study performed in order to evaluate the effect of ramelteon on QT intervals.

A total of 56 patients were enrolled in this study. Baseline ECG readings were obtained at the following intervals after dosing with placebo on the first day prior to each treatment sequence: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16 and 24 hours.

Participants received 4 treatment sequences: placebo, ramelteon 32 mg, ramelteon 64 mg, moxifloxacin 400 mg (positive control). ECG readings were obtained on Days 1 and 6 following treatment dosing.

The QTc data (Frederica formula) were analyzed using:

- Mean change from baseline on Day 1 and Day 6
- The maximum mean change from baseline on Day 1 and Day 6
- Change from baseline at T_{max} on Day 1 and day 6
    - This value was an average of 3 distinct QTc values: the individual subject value at T max, the value at 1 time point before the T max and the value at one time point after the Tmax

The positive control produced statistically significant increases in the mean change from baseline QTc values compared to placebo on Day 1 and Day 6. The ramelteon doses studied showed produced statistically significant decreases in the mean change from baseline QTc values compared to placebo on Day 6 only. Similar results were obtained when the maximum change data and the Tmax values were used in the analysis. Additionally, the findings held true when alternate QTc correction methods were used such as Bazett formula, Sagie formula or individual custom correction.

When given at doses 4- and 8- times the recommended dose, ramelteon did not prolong repolarization.

Table 39: Mean, Maximum and average of 3 values around T max for QTC (Fridericia formula)

QTc (msec)	Placebo (n=54)	Ramelteon 32 mg (n=54)	Ramelteon 64 mg (n=54)	Moxifloxacin 400 mg (n=54)
Daily mean QTc				
Baseline mean±SD	393±12	393±12	393±12	393±12
Day 1 mean±SD change from Baseline	-2.1±5.6	-1.7±6.3	-1.4±7.1	6.4±6.9*
Day 6 mean±SD change from Baseline	-1.2±5.8	-3.8±6.7*	-3.2±5.7*	8.0±7.4*
Daily maximum QTc				
Baseline mean±SD	393±12	393±12	393±12	393±12
Day 1 mean±SD change from Baseline	9.9±6.6	10.1±7.2*	11.2±8.3*	20.8±7.8*
Day 6 mean±SD change from Baseline	11.6±9.1	9.0±7.6*	8.8±8.9*	22.2±9.3*
Daily Tmax mean QTc				
Baseline mean±SD	393±12	393±12	393±12	393±12
Day 1 mean±SD change from Baseline	0.4±6.4	-1.5±8.0	-1.3±7.5	11.4±8.7*
Day 6 mean±SD change from Baseline	1.6±8.0	-4.3±8.1*	-3.7±7.2*	13.1±9.4*

Source: Tables 14.2.1.3-14.2.1.8 in TL040.

*P<0.05 vs. placebo using Dunnett pairwise t-test within analysis of variance per Table 14.2.1.6.
(Table taken from IAS, p.166, source tables were 14.2.1.4-14.2.1.8 in study report for TL040)

Table 40: Subjects with ECG changes (prespecified values) =on Day 6

	Placebo (n=54)	Ramelteon 32 mg (n=54)	Ramelteon 64mg (n=54)	Moxifloxicin 400mg (n=54)
QTc (msec) Fridericia				
Males: <430	28 (51.9%)	28 (51.9%)	28 (51.9%)	27 (50.0%)
Males 430-450	0	0	0	1 (1.9%)
Males >450	0	0	0	0
Females: <450	26 (48.1%)	26 (48.1%)	26 (48.1%)	26 (48.1%)
Females 450-470	0	0	0	0
Females >470	0	0	0	0
QTc increase 30-59 msec	3 (5.6%)	0	1 (1.9%)	12 (22.2%)
PR > 25% mean change	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)
QRS > 25% mean change	0	1 (1.9%)	1 (1.9%)	1 (1.9%)
HR > 25% decrease and < 50 bpm	0	0	1 (1.9%)	0

(Table 14.2.1.33-14.2.1.36 from study report)

7.1.10 Immunogenicity

There was no immunogenicity data provided to assess the impact of immunogenicity on safety, efficacy, clinical pharmacokinetics or pharmacology. While any drug product may elicit an idiosyncratic hypersensitivity response, there is no evidence that this product has any increased potential for producing such reactions.

During the development program one patient was discontinued early due to a Type I hypersensitivity reaction. Subject 12153/1028 was a participant in study TL007, a drug interaction study (ramelteon and ketoconazole). She was noted to have allergic rhinitis and allergic dermatitis after 2 days of ketoconazole administration, 1 days after receiving 16 mg of ramelteon. She was given 25 mg of IM diphenhydramine as treatment. She was also noted to have eosinophilia. She had been noted to have elevated eosinophils on Day -1, with a level of 7.8% (normal range 0-5%), and she reached a peak level of 14% 18 days after receiving 16 mg of ramelteon (Day 21). She was withdrawn from the study due to the eosinophilia.

[*Reviewer's note: I reviewed the CRF for this patient: Subject 12153/1028. While I agree with the sponsor's assessment that the event was treatment emergent-I am not certain that there is a true causal relationship with the ramelteon dose. I would be inclined to attribute the hypersensitivity to the ketoconazole which she had received for the 48 hours preceding her reaction.*]

7.1.11 Human Carcinogenicity

No formal carcinogenity studies were done in humans. In the preclinical development plan, tumors were seen in both the rat and the mouse models: tumors of the Hardarian gland along with hepatocellular adenomas and carcinomas in mice and Leydig cell tumors along with hepatocellular adenomas and carcinomas in the rat.

I performed a search of the adverse events database provided at the 120-day safety update and found 20 patients listed under the SOC heading "Neoplasms benign, malignant and unspecified (incl cysts and polyps). " I have provided the information in tabular form below.

Table 41: Neoplasms detected during the development program

Study	Subject ID	Sex	Age	Verbatim term for AE	Dose	Study Day
005	12074/2042	Female	32	Acute Lung Cancer	4-32 mg	30
021	12676/211019	Female	57	Basal Cell Carcinoma	16 mg	15
022	09843/221063	Female	47	Worsening Of Uterine Fibroids	16 mg	52
022	10153/202276	Male	62	Pain L Heel Secondary To Wart	16 mg	165
022	10420/221403	Female	40	R Shoulder Lipoma	16 mg	93
022	10420/222102	Male	68	Prostate Cancer	8 mg	66
022	12074/170154	Male	72	Colon Cancer	8 mg	118
022	12676/211022	Female	32	Uterine Fibroid Tumors	16 mg	288
022	12704/221505	Female	49	Brain Stem Tumor	16 mg	50
022	12704/251141	Male	82	Bladder Cancer	8 mg	169
022	12720/221110	Female	48	Uterine Fibroids	16 mg	84

Study	Subject ID	Sex	Age	Verbatim term for AE	Dose	Study Day
022	12817/221265	Female	29	Prolactinoma	16 mg	229
022	12823/221174	Female	64	L Shoulder Cyst	16 mg	.
022	20768/221481	Female	52	Ruptured L Knee Cyst	16 mg	27
022	20768/221491	Male	53	Two Gallbladder Polyps Per Ultrasound	16 mg	69
025	12820/251839	Male	72	Basal Cell Carcinoma	4 mg	37
025	12825/251531	Male	78	White Bump-Inner Lower Left Eyelid	8 mg	15
025	20369/251563	Female	66	Excision Basal Cell Carcinoma (Worsening)	4 mg	16
025	20374/251457	Male	78	Basal Cell Right Upper Chest	8 mg	15
025	20757/251802	Male	67	Lump On (L) Palm Below Finger	4 mg	25
025	20757/251802	Male	67	Lump On (R) Mid Knuckle	4 mg	25
025	20757/251802	Male	67	Lump On Mid Back (R) Of Spinal Column	4 mg	27

The only one of the tumors listed below that I found to be of concern in light of the known ramelteon use was the prolactinoma seen in patient 12817/221265. The findings from this case were previously discussed in section 7.1.6. I note that all twenty of the listed patients had received ramelteon and there were no neoplasms reported from the placebo group. I am not certain that the currently available data would allow us to attribute causality to ramelteon use or even to postulate that it might be the case.

7.1.12 Special Safety Studies (Endocrine)

Due to concerns about ramelteon's possible endocrine effects, studies TL031, TL022, and TL032 included evaluation of endocrine parameters.

Dr. Mary Parks, of the Division of Metabolic and Endocrine Drug Products, performed a consult on the provided data. I have summarized her remarks below:

TL-031: a four week placebo controlled study in adults

- Adrenal axis: There were no significant differences in the mean changes from baseline to Week 4 for ACTH or morning cortisol levels.
- Thyroid axis: There were no significant differences in the mean changes from baseline to week 4 in T4 (free and total), T3 and TSH levels between the two treatment groups.
- Reproductive axis: There were no significant differences in the mean changes from baseline to week 4 for testosterone (free and total), estradiol, prolactin, FSH or LH levels between the two treatment groups.

Conclusion: Though an effect of ramelteon on the endocrine system is unlikely to be detected in this short study, there were no significant changes in the measured endocrine parameters from baseline to Week 4. Evaluation of individual patient data which was reported as out of range did not reveal clinically significant changes for any given patient.

TL-032: a 6-month placebo-controlled parallel group study in adult patients

- Adrenal axis: There were no significant differences in the mean changes from baseline to Week 4 for ACTH or morning cortisol levels.
- Thyroid axis: There were no significant differences in the mean changes from baseline to week 4 in T4 (free and total), T3 and TSH levels between the two treatment groups.

- Reproductive axis: There were no significant differences in the mean changes from baseline to week 4 for testosterone (free and total), estradiol, FSH or LH levels between the two treatment groups.

  There was no statistically significant change seen in the effect of treatment over time in total testosterone, estradiol, FSH, or LH. Evaluations of free testosterone revealed a statistically significant difference in the mean change from baseline during month one; the mean increase from baseline in the ramelteon group was 21.6 pg/mL.

  A statistically significant difference in the mean change from baseline for prolactin levels was observed when the active drug group was compared with the placebo arm, p=0.003: mean change for the ramelteon group was +2.9 microgram/L, mean change for the placebo group was -0.6 microgram/L. When evaluated by individual month, the statistically significant differences were noted to occur at Month 1 (mean change for the ramelteon group was +3.7 microgram/L, mean change for the placebo group was -0.8 microgram/L) and Month 4 (mean change for the ramelteon group was +2.5 microgram/L, mean change for the placebo group was -0.1 microgram/L).

  While both treatment arms had patients whose prolactin levels switched from low/normal at baseline to high during the study, the proportion of patients doing so was higher in the active treatment arm (10.9% vs. 3.6% at Month 1; 9.5% vs. 3.9% at month 2; 16.7% vs. 9.1% at Month 4.)

Conclusion: Further evaluation of ramelteon's effects on prolactin and the long-term consequence on reproductive and bone health should be considered.

TL-022: a 12-month open-label study in adult and elderly patients

- Thyroid axis: While 6% of the patients had abnormal TSH values in study TL-375-022, only a few would have met the criteria for a primary thyroid disorder. Although there is not a control group embedded in this study, the incidence of thyroid abnormality is similar to the placebo rate seen in the other studies.
- Reproductive axis: No conclusions may be made regarding changes in testosterone levels in this study. The incidence of low testosterone levels is similar to that seen in the placebo-controlled studies.
- Adrenal axis: There were two patients who were noted to have abnormal morning cortisol and subsequently abnormal ACTH stimulation testing. This finding was not present in either of the placebo-controlled studies.

Conclusion: It is difficult to make any conclusions based upon the results of this open-label, uncontrolled study.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.13.1 Drug withdrawal effects

Studies TL020, TL021 and TL025 all used the benzodiazepine withdrawal scale questionnaire (BWSQ) to assess subjective withdrawal symptoms after abrupt drug discontinuation. There was no evidence of drug withdrawal symptoms as measured by the BWSQ in the adult and elderly participants in these studies.

Table 42: Chronic insomnia studies-BWSQ scores

		Ramelteon		
	Placebo	**4 mg**	**8 mg**	**16 mg**
TL020; parallel-group study, 35 nights, adults				
N	239	--	230	233
Change in BWSQ score on Day 7 off-treatment	0.0	--	-0.1	-0.1
TL021; parallel-group study, 35 nights, adults				
N	118	--	121	127
Change in BWSQ score on Day 2 off-treatment	-0.1	--	-0.2	-0.1
TL025; parallel-group study, 35 nights, elderly				
N	228	232	237	--
Change in BWSQ score on Day 7 off-treatment	-0.1	-0.1	-0.2	--

Source: [8] study report, Table 14.2.11.2; [9] study report, Table 14.2.21.2; and [11] study report Table 14.2.11.4.
-- indicates not done.
Table 16 a from the IAS

7.1.13.2 Rebound insomnia

Rebound insomnia is a particular type of drug withdrawal effect, characterized by a worsening of insomnia after a sedative/hypnotic has been discontinued. The sponsor evaluated this in three studies, comparing the last on treatment sleep latency to the sleep latency measured during the placebo washout period.

Study TL020 and TL021 both enrolled adult patients and administered study drug for 35 nights. In TL020, no statistically or clinically significant differences on sSL were seen during the 7-day placebo washout period. In TL021, there was a greater decrease in LPS for the ramelteon 8 mg group than the placebo group rather than an increase. On day 2 the change from baseline values was not statistically significant.

Study TL025 enrolled elderly patients and administered study drug for 35 nights. In TL025, there were statistically significant differences in sSL for ramelteon 4 and 8 mg on the first day off-treatment, and for ramelteon 8mg at 2 and 6 days off treatment. The changes were greater decreases in sleep latency for the ramelteon groups compared to placebo rather than an increase. The change from baseline was not significant by day 7.

Table 43: changes from baseline following treatment

		Ramelteon		
	Placebo	**4 mg**	**8 mg**	**16 mg**
TL020; 35 nights, adults				
N	200	--	193	193
Change in sSL on Day 7 off-treatment (min)	-22.3	--	-27.7	-24.5
P-value for difference from placebo			0.527	0.739
TL021; 35 nights, adults				
Day 1 off-treatment				
N	118	--	124	128
Change in LPS (min)	-20.0	--	-33.1	-30.3
P-value for difference from placebo		--	*0.007	0.081
Day 2 off-treatment				
N	116	--	121	128
Change in LPS (min)	-31.8	--	-21.0	-32.1
P-value for difference from placebo		--	0.249	0.771
TL025; 35 nights, elderly				
N	180	194	200	--
Change in sSL on Day 7 off-treatment (min)	-20.9	-22.0	-29.5	--
P-value for difference from placebo		0.797	0.322	

Source: [8] study report, Tables 14.2.10.1 and 14.2.20.1; [9] study report, Tables; and [11] study report, Tables 14.2.10.2.
-- indicates dose not studied. P-values based on least square mean differences.
*=statistically significant
Table 16 b from the IAS

7.1.13.3 Next-day residual effects

The sponsor assessed next-day residual effects by comparing baseline responses to those from the morning following drug use using the following parameters:

- Alertness and attention using the digit symbol substitution test (DSST)
- Subjective feelings (related to sedation) and mood using a visual analog scale
- Memory using either the word list memory test or the memory recall test
- Postsleep questionnaire addressing the level of alertness and ability to concentrate

The studies, which used doses ranging from 4 to 64 mg evaluated residual effects that were measured the morning following a night in the sleep laboratory.

In the 2 night crossover studies of chronic insomnia, TL005, which used doses of 4, 8, 16 and 32 mg, and TL017, which used doses of 4 and 8 mg, there was no evidence of next-day residual effects on any of the measurements used.

In study TL021, a double-blind, placebo-controlled, parallel group study in adults with chronic insomnia, ramelteon (8 or 16 mg) was administered for 35 nights. Measures of residual effects

were done on Nights 1 and 2 representing week 1, nights 15 and 16 representing week 3 and nights 29 and 30 representing week 5. At week 1, patients who received 8 mg ramelteon had improved ability to concentrate, a lower score for delayed recall, and a VAS score indicating more fatigue in comparison to placebo. At week 3, patients who received 8 mg ramelteon had a lower score for immediate recall, and a VAS score indicating more sluggishness in comparison to placebo. These findings were not apparent in the patients who recovered 16 mg of ramelteon. Neither ramelteon dose had next-morning residual effects different from placebo at Week 5.

7.1.13.4 Abuse potential

The sponsor performed two studies to assess the abuse potential of ramelteon: TL014 and TL015.

In study TL014, a dose-finding study, ascending doses of ramelteon were administered to 6 subjects with a history of substance abuse or dependence. There were eight treatment periods. Subjects received one dose of the following in a randomized sequence: placebo, triazolam 0.25 mg, triazolam 0.75 mg. During the remaining five treatment periods, subjects received ramelteon in ascending doses: 16 mg, 32 mg, 64 mg, 96 mg and 128 mg. The potential abuse liability was assessed using the following instruments: Next Day Questionnaire, Addiction Center Research Inventory, Drug Effect Questionnaire, Subjective Effects questionnaire, Observer Rated Questionnaire and Pharmacologic Class Questionnaire. The study subjects were unable to distinguish ramelteon, at doses up to and including 132 mg, from placebo. No subject had difficulty distinguishing the 0.75 mg dose of triazolam from placebo.

Pharmacodynamic effects were assessed in study TL014: an alertness VAS was completed by subject and observer at 8 time points in the first 12 hours post dose and at 24 hours postdose, Word List Memory Test was administered at 2 and 6 hours postdose and DSST at 7 time points in the first 12 hours post dose and at 24 hours postdose. At all doses the results after ramelteon use were similar to placebo.

In study TL015, a double-blind, placebo-controlled, 7-period crossover study, ramelteon was administered to 14 subjects with a history of hypnotic or anxiolytic abuse/dependence. There were seven treatment periods. Subjects received one dose of the following in a randomized sequence: placebo, triazolam 0.25 mg, triazolam 0.5 mg, triazolam 0.75 mg, ramelteon 16 mg, 80 mg and 160 mg. The potential abuse liability was assessed using the following instruments: Next Day Questionnaire, Addiction Center Research Inventory, Drug Effect Questionnaire, Subjective Effects questionnaire, Observer Rated Questionnaire and Pharmacologic Class Questionnaire. The study subjects thought ramelteon was similar to placebo, at doses up to and including 160 mg. Dose-related responses of preference/liking were seen with triazolam at the higher two doses studied.

Pharmacodynamic effects were assessed in study TL015. A Word recall/recognition task was administered at 2 and 6 hours postdose. The following tests were administered at 1, 2, 3, 4, 6, 8, 12 and 24 hours post dose: DSST, an enter and recall test which required keypad entry of randomly displayed 8 digit numbers, a balance task which required that a subject stand upright

on one foot with closed eyes, a circular lights task which required that the subject press a series of 16 buttons in response to the random illumination of their associated lights. An alertness VAS was completed by the subject at 8 time points in the first 12 hours post dose and at 24 hours postdose. At all doses the results after ramelteon use were similar to placebo.

7.1.14 Human Reproduction and Pregnancy Data

The sponsor did not perform any studies to assess potential effects of ramelteon on human reproduction, pregnancy or development.

However during the course of the development program, eleven women became pregnant: 4 of whom had received placebo. In all eleven cases, the women discontinued the study once they had been found to have a positive pregnancy test:

Placebo group

- Subject 12645/201690, who was randomized to placebo, received the first dose of double-blind study medication on 06 June 2003. Her last menstrual period was on [ ]. The first positive pregnancy test was on [ ] and ultrasound confirmed the presence of a fetus on [ ] The delivery date was [ ] The subject had an uncomplicated vaginal delivery of a live infant. No Apgar scores were provided. [Study 020]
- Subject 09894/037 had received placebo from 20 June 2003 to 26 June 2003. Her pregnancy was confirmed on [ ] prior to randomization. She was withdrawn from the study [ ] The mother had mild pregnancy-induced hypertension. She delivered an apparently healthy baby girl on [ ] [Study 021]
- Subject 20650/321134 had been randomized to placebo. She ingested study drug from 07 July 2003 to 20 December 2003. She completed the study and ingested her last dose of study drug on Day [ ] Her pregnancy test was positive on [ ] She had an estimated delivery date of [ ] [Study 032]
- Subject 20651/321329 had been randomized to placebo. She ingested study drug from 18 November 2003 to 03 May 2004. Her pregnancy test was positive on [ ] She had a spontaneous abortion on [ ] [Study 032]

Ramelteon group

- Subject 12820/201254, who was randomized to 8 mg, received the first dose of double-blind study medication on 20 March 2003. Her last menstrual period was on [ ]. She completed the study, discontinuing the study medication as per protocol on Day 35. The first positive pregnancy test was on [ ] The subject declined to provide further information about her pregnancy and refused follow-up contact from the investigator. No further information is available. [Study 020]

- Subject 12721/211327 had been randomized to ramelteon 8 mg. She ingested study drug from 9 June 2003 to 22 July 2003. Her pregnancy was confirmed on [ ] which was [ ]; after she completed the study. She had an induced abortion on [ ] [Study 021]
- Subject 12861/221152 had been randomized to ramelteon 16 mg. She ingested study drug from 5 June 2003 to 30 September 2003. Her pregnancy was confirmed on [ ] She reported having had an induced abortion the same day. Study drug was discontinued on [ ] The results of a qualitative serum beta HCG were positive 2 weeks later. On Day 127, she signed a letter withdrawing study consent and refusing further follow-up. [Study 022]
- Subject 10420/221462 had been randomized to ramelteon 16 mg. She ingested study drug from 10 September 2003 to 04 January 2004. Her pregnancy test was positive on [ ] Study drug was discontinued on Day — and she was withdrawn from the study on Day — She delivered a [ ] child on [ ] [Study 022]
- Subject 12676/211021 had been randomized to ramelteon 16 mg. She ingested study drug from 28 March 2003 to 23 April 2003. She had a positive pregnancy test on [ ] She underwent laparoscopic surgery to remove the ectopic pregnancy on [ ] Study 022]
- Subject 12944/281007 had ingested placebo during period 1 followed by ramelteon 32 mg in combination with alcohol 0.6g/kg in period 2. Her pregnancy was confirmed on [ ] She had an induced abortion on [ ] [Study 028]
- Subject 12676/221283 had been randomized to ramelteon 16 mg. She ingested study drug from 13 August 2003 to 05 November 2003. Her pregnancy test was positive on [ ] She was discontinued from the study having taken the last dose of study drug on day —. She had a spontaneous abortion on [ ]. [Study 022]
- While randomized to receive ramelteon, Subject 12700/019 had not received any study medication prior to the detection of her pregnancy. No additional information is available on the course of her pregnancy or its outcome. [Study 021]

The sponsor is not recommending the use of ramelteon during pregnancy or lactation.

7.1.15 Assessment of Effect on Growth

This section is not applicable for this NDA submission as the drug was not studied in children.

7.1.16 Overdose Experience

There were no reported incidences of overdose during the development program.

The studies used doses ranging from 4 mg (half the recommended dose) to 160 milligrams (20 times the recommended dose). There was no clear escalation of adverse events with escalation in dose.

Systemic exposure was noted to increase 190-fold when fluvoxamine was taken in association with ramelteon. Subjects who took the combination had an increased incidence of nausea/vomiting, diarrhea, dizziness, and dysphoria. The current approved labeling for fluvoxamine includes all of these adverse events except dysphoria. While the dysphoria may be attributed at least in part to the concomitant drug dosing, it is difficult to determine whether the concomitant drug dosing was responsible for the other symptoms.

There is no known antidote to be used in the event of an apparent ramelteon overdose. Hemodialysis does not reduce exposure to ramelteon and so cannot be recommended as treatment for suspected overdose.

7.1.17 Postmarketing Experience

This section is not applicable for this NDA submission as the drug has not yet been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This was an extensive development plan which utilized multiple types of study designs.

The full listing of all clinical studies including study type and patient enumeration has been provided in section 4.2 and will not be reproduced here.

7.2.1.2 Demographics

Table 44: Demographics for Phase I to III studies

	Placebo (n=1370)	**<4mg (n=20)**	**4 mg (n=511)**	**8mg (n=1250)**	**16mg (n=1961)**	**32mg (n=169)**	**64mg (n=209)**
Age (years)							
All (+/- SD)	48.6 +/- 18.2	30.2 +/- 7.0	629 +/- 17.1	30.2 +/- 7.0	30.2 +/- 7.0	30.2 +/- 7.0	30.2 +/- 7.0
<65 years	978 (71.4%)	20 (100%)	131 (25.6%)	629 (50.3%)	1937 (98.8%)	169 (100%)	208 (99.5%)
≥65 years	392 (28.6%)	0	380 (74.4%)	621 (49.7%)	24 (1.2%)	0	1 (<1%)
Gender							
Male	557 (40.4%)	20 (100%)	200 (39.1%)	530 (42.4%)	811 (41.1%)	70 (41.4%)	106 (50.7%)
Female	813 (59.3%)	0	311 (60.4%)	720 (57.6%)	1150 (58.6%)	99 (58.6%)	103 (49.3%)
Ethnicity							
Caucasian	999 (72.9%)	18 (90%)	422 (82.6%)	965 (77.2%)	1467 (76.3%)	68 (40.2%)	134 (64.1%)
Black	128 (9.3%)	0	38 (7.4%)	130 (10.4%)	221 (11.3%)	24 (14.2%)	17 (8.1%)
Hispanic	207 (15.1%)	0	44 (8.6%)	120 (9.6%)	187 (9.5%)	76 (45.0%)	56 (26.8%)
Asian	24 (1.8%)	1 (5%)	2 (<1%)	21 (2%)	36 (2%)	24 (2%)	1 (1%)
Other	12 (<1%)	1 (5%)	5 (1%)	14 (1%)	20 (1%)	0	1 (<1%)

(modification of Table 4.a from the Integrated Analysis of Safety)

7.2.1.3 Extent of exposure (dose/duration)

At the time of the 120 day safety update, 165 subjects had been exposed to ramelteon for periods of 330 days or more. In the placebo group, the maximum was 190 days. In the ramelteon group, the maximum was 362 days.

Table 45: Exposure by dose and duration across all Phase I through Phase III studies (IAS data)

Exposure (days)	Placebo	<4mg	4mg	8 mg	16mg	32mg	64mg
N	1361	20	511	1250	1961	169	209
Mean	24.3	1.0	18.5	51.2	58.5	3.3	2.9
SD	31.51	0.00	16.27	81.0	65.36	1.93	2.55
1 day	306 (22.3%)	20 (100%)	27 (5.3%)	122 (9.8%)	320 (16.3%)	8 (4.7%)	134 (64.1%)
>1 - 7 days	281 (20.5%)	0	216 (42.3%)	244 (19.5%)	253 (12.9%)	161 (95.3%)	75 (35.9%)
>7 - 35 days	545 (39.8%)	0	220 (43%)	562 (45%)	516 (26.3%)	0	0
>35 - 180 days	223 (16.3%)	0	48 (9.4%)	278 (22.2%)	715 (36.5%)	0	0
>180 days	6 (0.4%)	0	0	34 (2.7%)	95 (4.8%)	0	0
Missing	9	0	0	10	62	0	0

(Table 22.1.2.1 from the Integrated Analysis of Safety)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were used in the evaluation of safety for this NDA submission.

7.2.2.2 Postmarketing experience

This section is not applicable for this NDA submission as the drug has not yet been marketed.

7.2.2.3 Literature

No studies from the literature were used in the evaluation of safety for this NDA submission.

7.2.3 Adequacy of Overall Clinical Experience

The placebo-controlled trials performed were adequate to assess the question of the drug effect on sleep latency (the primary objective).

This application exposed an adequate number of subjects (n >3000) to this new formulation. The gender ratio was appropriate. While it may have been desirable to achieve greater ethnic diversity in the population studies, that is a problem endemic to clinical trials and not specific to this development program.

Overall the inclusion exclusion criteria were appropriate. Patients with severe or chronically progressive renal or hepatic disease would have been excluded from the general trials but the sponsor performed targeted studies in those populations. Patients with severe or unstable respiratory insufficiency were excluded from study participation. However, the sponsor performed studies in patients with mild-to-moderate sleep apnea and with mild-to-moderate COPD.

The doses and durations of exposure were adequate to assess safety for the intended use of this product. The sponsor appropriately evaluated participants for next-day residual and rebound effects which have been associated with use of the sedative/hypnotics.

The preclinical testing had revealed that there were potential endocrine effects of ramelteon use. The sponsor addressed these potential effects in humans through measuring endocrine parameters in three studies as has been previously discussed. In light of the elevated prolactin levels found in Study 032, measurement of prolactin levels should have been included in study TL-022. While it would have been optimal had Study TL-022 been a placebo-controlled study, it would have been difficult to perform such a long-term study without a significant number of discontinuations.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pre-clinical testing was adequate to explore general toxicity as well as reproductive toxicity. Special studies were performed to assess endocrine effects in rodent models. While increased levels of circulating melatonin were detected after 4 weeks of dosing, the sponsor did not evaluate whether those levels returned to baseline with cessation of drug use. The latter determination may have provided further insight into the mechanism of drug action.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing done was adequate and appropriate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Takeda evaluated ramelteon both as a substrate for interactions (interference with its clearance) and as an inducer or inhibitor of the clearance of other drugs.

The studies performed, as detailed in Section 7.4.2.4, were adequate to assess:

- The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways
- The effect of the drug on CYP450 enzymes (inhibition, induction)
- The potential safety consequences of drug-drug interactions

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The class specific adverse events of concern are the next-day residual effects and the rebound effect after abrupt drug discontinuation. The sponsor adequately assessed the study participants for these effects as detailed in section 7.1.12.

While it would be good to know if a given surrogate/hypnotic drug has any next-day effect on driving ability, the studies of vigilance and alertness that were done may be considered a sort of surrogate marker for that specific task. Sponsors are currently trying to devise a safe manner of specifically testing driving ability in patients using sedative/hypnotics.

7.2.8 Assessment of Quality and Completeness of Data

Each of the individual study reports reviewed appeared to be complete.

In some of the listing, such as the narratives, errors such as repeated patient numbers were found, e.g. Subject 12708/221002, as described in the discontinuations section of this review.

There were inconsistencies between some of the tables and data presented elsewhere in the submission: in table 5a (on page 44/6084 of the IAS) which lists subject disposition, one death is reported and 4 pregnancies are reported as reasons for discontinuation. Elsewhere in the IAS, narratives are given for two deaths and eleven pregnancies, all 13 events represented study discontinuations.
[*Reviewer's note: We mentioned this inconsistency to the company on May 31st, they have told us that they will look into it and appraise us of their findings. The information presented in this review as well as the narrative section of the NDA submission is correct.*]

The sponsor elected to provide "treatment-emergent" adverse events only. Within the IAS, the sponsor omitted from the listings all adverse events which were not felt to be treatment emergent. Adverse events which occurred after 7 days were collected and have been discussed in section 7.4.2.2.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update was an interim report of the data from the ongoing study TL-022. The results from this update have been incorporated into the body of the review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Ramelteon is capable of producing adverse effects such as:

Headache
Most of the cases reported were considered mild-to moderate in severity by the investigators.

Somnolence
Most of the cases reported were considered mild-to moderate in severity by the investigators.

Fatigue
Most of the cases reported were considered mild-to moderate in severity by the investigators.

Nausea
Most of the cases reported were considered mild-to moderate in severity by the investigators.

Dizziness
Most of the cases reported were considered mild-to moderate in severity by the investigators.

Additionally, ramelteon use may be associated with hyperprolactinemia, visual disturbance/eye pain, abnormal liver function tests. Nightmares and hallucinations were rarely reported in association with ramelteon use.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The sponsor provided analyses of the subject pool in multiple different permutations, as detailed in the next section. The incidence estimates provided earlier were based upon the pooled results from the Phase I to III studies.

I have no done further pooling to include the drug interaction studies, the Japanese studies or the disease-interactions studies as I felt that to do so might introduce further confounders in the assessment of adverse events.

7.4.1.2 Combining data

The sponsor pooled the data into 6 study groups for evaluation in the Integrated Analysis of Safety, combining the numerator events and denominators for the selected studies.

1. Phase I to Phase III studies (n=18)
    a. Chronic insomnia studies (listed below)
    b. Healthy volunteer studies (listed below)
    c. 6-month endocrine study (TL032)
    d. Long term safety study (TL022)
2. Placebo-controlled chronic insomnia studies (5):

TL005, TL017, TL020, TL021, TL025

3. Healthy volunteer studies (11):
   PNFP001, PNFP002, TL003, TL004, TK006, TL023, TL031, TL040, EC002, EC003, EC004
4. Drug interaction studies(n=13):
   TL007, TL008, TL009, TL024, TL026, TL027, TL028, TL033, TL034, TL035, TL036, TL037, TL043
5. Japanese studies (N=5):
   CPH001, CPH002, CPH003, CPH005, CPH006
6. Disease-interaction studies (n=6):
   TL014, TL015, TL029, TL030, TL038, TL039

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

There were no explorations for dose dependency other than those previously discussed.

7.4.2.2 Explorations for time dependency for adverse findings

Overall there were very few post-treatment adverse events, defined as events occurring on post-treatment day 8 or later. Fewer than 5% of the placebo patients (4.1%) had such events while just slightly over 5% of the all ramelteon group did (5.6%). The highest proportion of late effects was seen in the 16 mg group (5.9%) followed by the <4 mg group (5%), the 8 mg group (4.7%), the 32mg group (3%) and the 64 mg group (2.4%). In the table below, I have presented selected late effects for the 4mg, 8 mg and 16 mg doses since those are the ones which are most likely to be commonly used clinically, although only the 8mg is proposed for marketing.

Table 46: Selected late effects for the 4mg, 8 mg and 16 mg doses of ramelteon

	Placebo	4 mg	8mg	16 mg
Leukocytosis	0	0	1 (0.1%)	0
Diarrhea	1 (0.1%)	0	0	2 (0.1%)
Nausea	0	0	3 (0.2%)	0
GI hemorrhage	0	1(0.2%)	0	0
Peripheral edema	0	0	4 (0.3%)	0
Fatigue	0	0	1 (0.1%)	2 (0.1%)
Fall	0	0	1 (0.1%)	1 (0.1%)
Headache NOS	6 (0.4%)	0	1 (0.1%)	7 (0.4%)
Dysgeusia	0	0	3 (0.2%)	0
Somnolence	2 (0.1%)	0	0	2 (0.1%)
Insomnia exacerbated	3 (0.2%)	0	5 (0.4%)	2 (0.1%)
Depression	0	0	2 (0.2%)	1 (0.1%)

(Data from Table 22.4.4.2 in the IAS)

7.4.2.3 Explorations for drug-demographic interactions

The majority of the participants in these trials were Caucasian; the small sample size for the other ethnicities makes it difficult to perform explorations for drug-demographic interactions.

There is no consistent evidence that age has an effect on the safety or efficacy of this product, however a subgroup analysis of adverse events by age did reveal that the proportion of the elderly who complained of anorexia, depression, and myalgia was higher than that of the non-elderly adults.

Subanalyses of adverse events divided by gender were done but the results were inconsistent and did not have true predictive value.

7.4.2.4 Explorations for drug-disease interactions

7.4.2.4.1 Hepatic impairment

The sponsor performed a study (TL029) of single and multiple doses of ramelteon in patients with mild (n=12) and moderate (n=12) hepatic impairment by Child-Pugh classification. Each patient group was matched for ethnicity, gender, weight, age and smoking status with 12 healthy subjects.

Study participants received a single dose 16 mg dose of ramelteon on Day 1 followed by a 2 day washout period before beginning serial dosing on Days 4 through 8.

Serum concentrations of ramelteon and its metabolites were measured on Days 1 and 8. Urine was collected to assess urinary excretion of ramelteon and its metabolites for 48 hours after dosing on Day 1 and for 24 hours after dosing on Day 8.

There was no apparent correlation between the degree of hepatic impairment and the level of increased exposure to ramelteon in patients with Child-Pugh scores between 5 and 8. Three (25%) of the patients with Child-Pugh scores of 9 (moderate hepatic impairment) were noted to have higher exposures to ramelteon than any other study subjects.

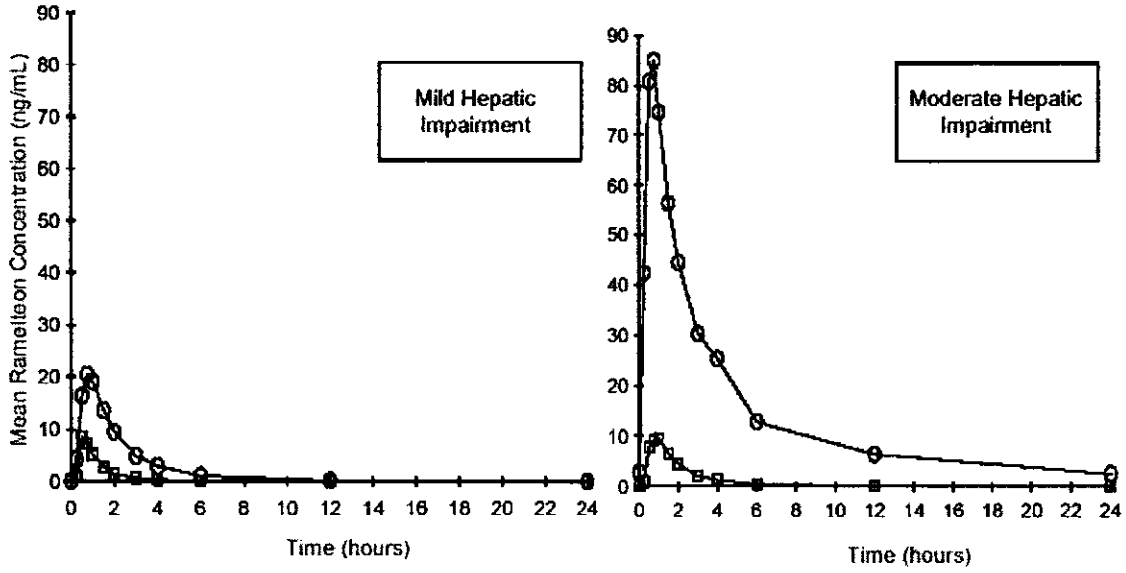
Ramelteon AUC values were 8 to 10.7 fold higher in patients with moderate hepatic impairment compared with healthy subjects. This increase in AUC values was not seen in patients with mild hepatic impairment.

The major circulating metabolite, M-II, had AUC values that increased less than 1.4-fold in subjects with mild to moderate impairment.

There were no differences in urinary excretion of ramelteon or M-II when patients were compared to healthy subjects.

The sponsor concluded that there were no clinically significant effects of the increased exposure in patients with moderate hepatic impairment due to ramelteon's wide margin of safety.

Figure 1: Serum concentration of ramelteon in patients with hepatic impairment



(Figure 2.e from module 2.7.2 of the NDA submission)

7.4.2.4.2 Renal impairment

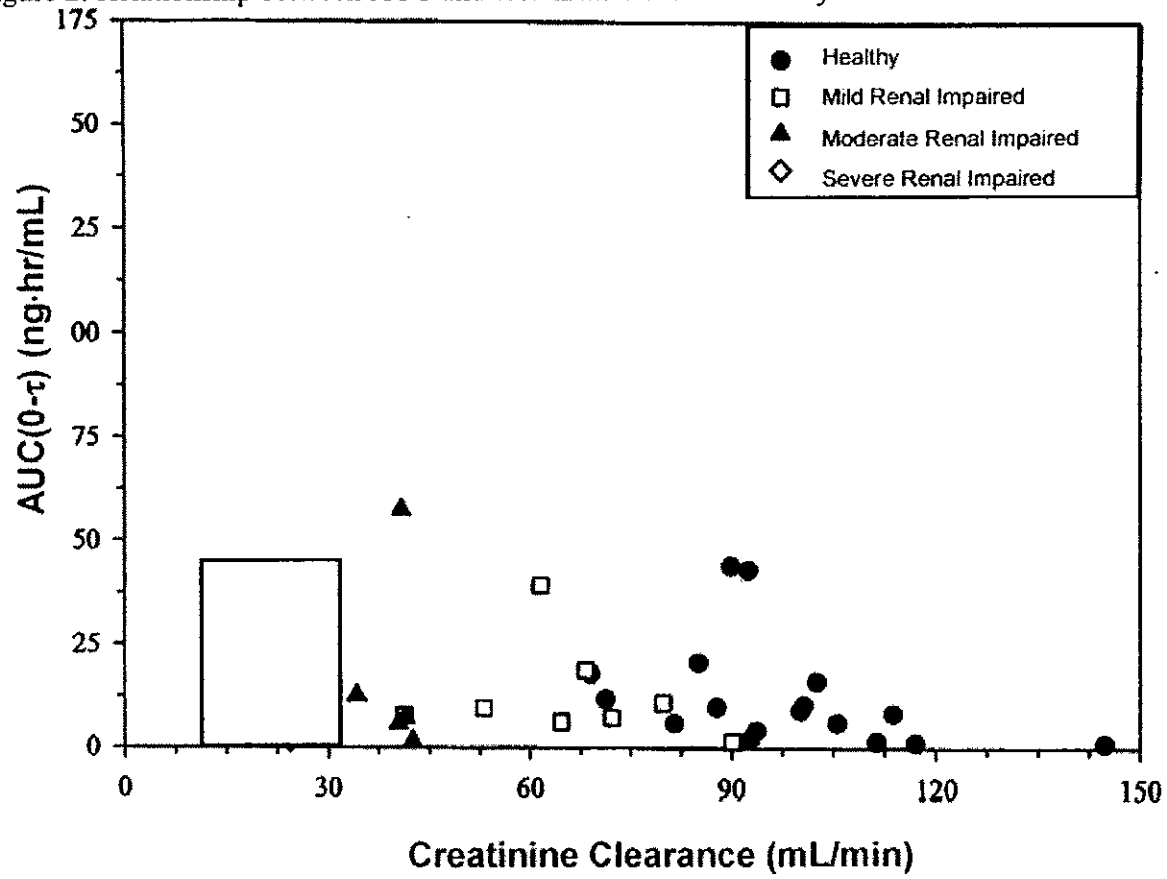
The sponsor performed a study (TL030) of single and multiple doses of ramelteon in patients with renal impairment: 8 with mild impairment, 5 with moderate impairment, 7 with severe impairment and 8 who required chronic hemodialysis. Each patient group was matched for ethnicity, gender, weight, age and smoking status with healthy subjects.

Study participants received a single dose 16 mg dose of ramelteon on Day 1 followed by a 2 day washout period before beginning serial dosing on Days 4 through 8.

Serum concentrations of ramelteon and its metabolites were measured on Days 1 and 8. Urine was collected to assess urinary excretion of ramelteon and its metabolites for 48 hours after dosing on Day 1 and for 24 hours after dosing on Day 8. Those subjects who received hemodialysis had dialysate samples collected for 4 hours post-dose for analysis of ramelteon and M-II.

No correlation between renal function, as determined by creatinine clearance, and ramelteon Cmax/AUC values was seen. While there were apparent differences between peak and total exposures to ramelteon when renal impairment patients were compared to healthy volunteers, the levels seen were within the therapeutic window for ramelteon.

Figure 2: Relationship between AUC and creatinine clearance on Day 8



(Figure 2.f from module 2.7.2 of the NDA submission)

Figure 3: Relationship between C_{max} and renal function on Day 8

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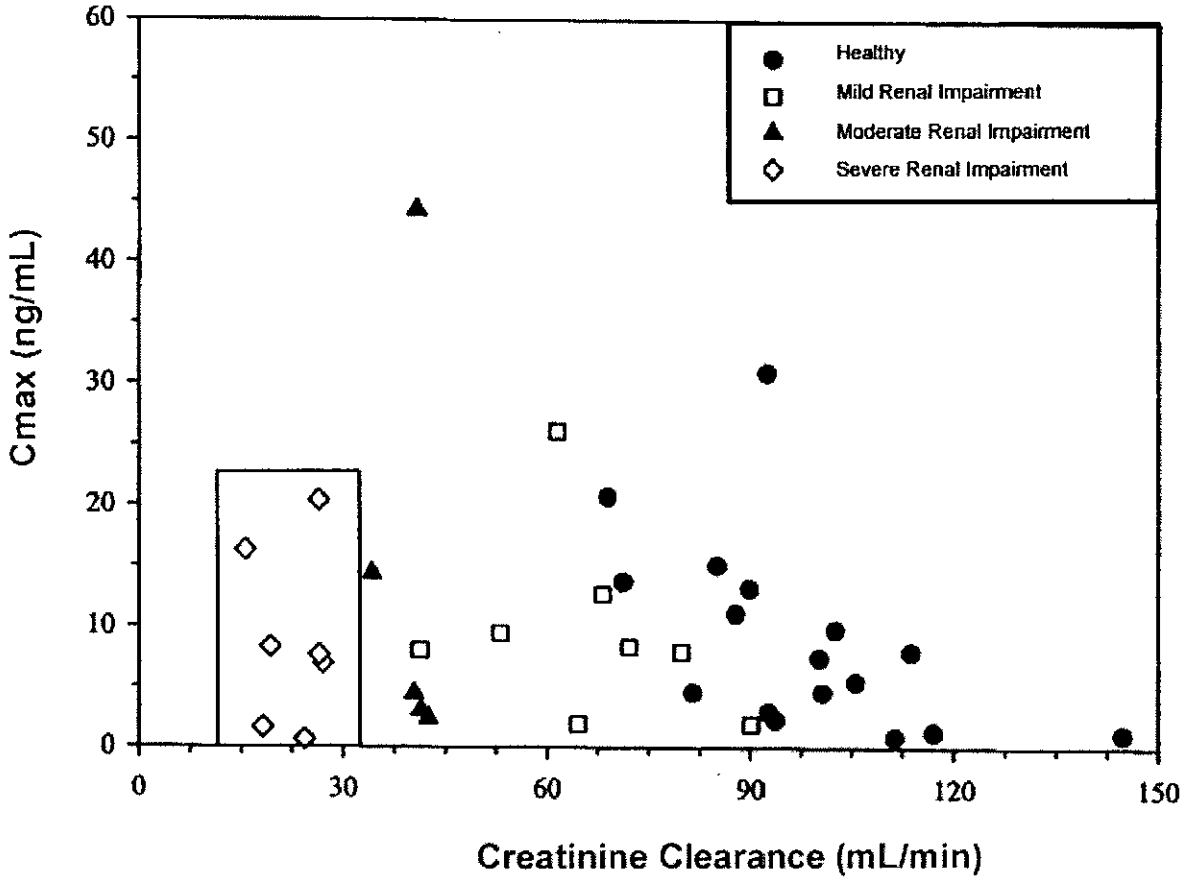

(Figure 2.g from module 2.7.2 of the NDA submission)

7.4.2.4.3 History of substance abuse

The results of studies TL014 and TL015, which evaluated ramelteon in association with ethanol, were discussed in Section 7.1.13: Withdrawal phenomena and/or abuse potential.

7.4.2.4.4 Chronic obstructive pulmonary disease, COPD (TL038)

The sponsor performed a Phase II, double-blind, placebo-controlled, single-dose 2-way crossover study (TL038) using a single dose of ramelteon 16 mg in 26 patients with mild to moderate chronic obstructive pulmonary disease.

The study participants were adults, aged 21 or older, with a clinical history of mild to moderate COPD. This diagnosis had to be confirmed by pulmonary function testing at screening. This study defined mild airflow limitation as 1) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) less than 70% and 2) FEV1 35%-75% of the predicted value accompanied by possible 3) chronic cough and sputum production. This study defined moderate airflow limitation as 1) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) less than 70% and 2) FEV1 35%-75% of the predicted value accompanied by possible 3) shortness of breath typically on exertion and 4) progression of symptoms.

All subjects were required to have an arterial oxygen percent saturation (SaO_2) greater than 85% during sleep for at least 99% of the recording period, with no SaO2 reading less than 80%. During periods of wakefulness, subjects were expected to have a SaO2 greater than 91% while sitting and while supine.

The primary outcome variable was the mean SaO2 for the entire night. No statistically significant difference in the primary variable was detected. Additionally, no deaths, SAEs, or discontinuations were reported during this study.

Table 47: summary of mean SaO2 for the entire night: ITT population

	Placebo	Ramelteon 16 mg
N	26	25
Min – Max	87.0 – 96.0	86.0 – 97.0
LS mean (SE)	92.9 (0.48)	92.9 (0.49)
LS mean difference from placebo (SE)		-0.0 (0.27)
95% CI of difference		(-0.6, 0.6)
P-value		0.972

(reproduced from the study report for TL-038)

7.4.2.4.5 Sleep apnea (TL039)

The sponsor performed a Phase II, double-blind, placebo-controlled, single-dose 2-way crossover study (TL039) using a single dose of ramelteon 16 mg in 26 patients with mild to moderate sleep apnea.

The study participants were adults, aged 21 to 64 years (inclusive), with a clinical history of mild to moderate obstructive or mixed sleep apnea with an apnea/hypopnea index (AHI) greater than or equal to 5 but less than or equal to 20.

The primary outcome variable was the AHI. No statistically significant difference in the primary variable was detected. Additionally, no deaths, SAEs, or discontinuations were reported during this study.

Table 48: summary of AHI: ITT population

AHI	Placebo	Ramelteon 16 mg
N	26	26
Min – Max	0.5 - 33.8	1.4 - 49.0
LS mean (SE)	11.1 (1.93)	11.4 (1.93)
LS mean difference from placebo (SE)		0.3 (1.13)
95% CI of difference		(-2.1, 2.6)
P-value		0.812

(reproduced from the study report for TL-039)

7.4.2.5 Explorations for drug-drug interactions

The sponsor evaluated most of the drug-drug interactions using oral doses of ramelteon. The 90% confidence interval was evaluated with an 80%-125% no-effect boundary, as per the FDA guidance for in vivo drug interaction studies.

7.4.2.5.1 Ketoconazole

TL007 was a randomized open-label crossover study to evaluate the effects of a CYP3A4 inhibitor on single-dose pharmacokinetics of ramelteon and its metabolites.

Subjects (n=28) were randomized into two treatment groups: Group A, who received nothing on days 1-3 and 16 mg of Ramelteon on Day 4 or Group B, who received ketoconazole 200 mg BID on Days 1-4 along with 16 mg of ramelteon on Day 4. After a 14-day washout, the subjects would crossover to the other therapy.

Blood and urine were collected before dosing and serially for 24 hours after dosing in order to evaluate serum concentration of ramelteon as well as urinary excretion of ramelteon and metabolites.

The T_{max} of ramelteon increased from a mean of 0.69 hours (when administered alone) to a mean of 1.02 hours when administered with ketoconazole: the difference was statistically significant, $p=0.005$. An 84% increase in the ramelteon AUC (0-∞), a 36% increase in ramelteon C_{max} and a 31% increase in ramelteon half-life were seen when co-administered with ketoconazole.

The T_{max} of M-II, the major ramelteon metabolite, increased from a mean of 0.9 hours (when ramelteon was administered alone) to a mean of 1.44 hours when ramelteon was administered with ketoconazole: the difference was statistically significant, $p<0.001$. An 93% increase in the M-II AUC (0-∞), a 23% increase in M-II C_{max} and a 52% increase in M-II half-life were seen when ramelteon was co-administered with ketoconazole.

The sponsor concluded that the results of this study confirmed that the CYP3A4 pathway is involved in ramelteon metabolism but that no dose adjustments were needed when ramelteon was co-administered with CYP3A4 inhibitors since the pharmacokinetic changes seen were not felt to be clinically meaningful.

7.4.2.5.2 Fluconazole

TL009 was a randomized open-label 2-period crossover study to evaluate the effects of a CYP2C9 inhibitor on single-dose pharmacokinetics of ramelteon and its metabolites.

Subjects (n=28) were randomized into two treatment groups: Group A, who received nothing on days 1-3 and 16 mg of ramelteon on Day 4 or Group B, who received fluconazole 400 mg QD on Day 1, fluconazole 200 mg QD on Days 2-4 along with 16 mg of ramelteon on Day 4. After a 14-day washout, the subjects would crossover to the other therapy.

Blood and urine were collected before dosing and serially for 24 hours after dosing in order to evaluate serum concentration of ramelteon as well as urinary excretion of ramelteon and metabolites. Separate blood samples were drawn to evaluate serum fluconazole concentration prior to each fluconazole dose.

A 152% increase in the ramelteon AUC (0-∞), a 144% increase in ramelteon C_{max} and a 33% increase in ramelteon half-life were seen when co-administered with fluconazole.

The T_{max} of M-II, the major ramelteon metabolite, was delayed by 19 minutes when ramelteon was administered with fluconazole: the difference was statistically significant, p=0.001. A 199% increase in the M-II AUC (0-∞), a 55% increase in M-II C_{max} and a 94% increase in M-II half-life were seen when ramelteon was co-administered with fluconazole.

The sponsor concluded that the results of this study confirmed that the CYP2C9 pathway is involved in ramelteon metabolism but that no dose adjustments were needed when ramelteon was co-administered with CYP2C9 inhibitors since the pharmacokinetic changes seen were not felt to be clinically meaningful.

7.4.2.5.3 Fluvoxamine

TL008 was a randomized open-label 2-period crossover study to evaluate the effects of a CYP1A2 inhibitor on single-dose pharmacokinetics of ramelteon and its metabolites.

Subjects (n=28) were randomized into two treatment groups: Group A, who received nothing on days 1-3 and 16 mg of ramelteon on Day 4 or Group B, who received fluvoxamine 100 mg BID on Days 1-4 along with 16 mg of ramelteon on Day 4. After a 14-day washout, the subjects would crossover to the other therapy.

Blood and urine were collected before dosing and serially for 24 hours after dosing in order to evaluate serum concentration of ramelteon as well as urinary excretion of ramelteon and metabolites. Separate blood samples were drawn to evaluate serum fluvoxamine concentration prior to each fluvoxamine dose.

A 190-fold increase in the ramelteon AUC (0-∞), a 70-fold increase in ramelteon C_{max} and a 3-fold increase in ramelteon half-life were seen when co-administered with fluconazole. A 99.6% reduction in drug clearance was also noted when ramelteon was administered with fluconazole.

The T_{max} of M-II, the major ramelteon metabolite, was delayed by 47 minutes when ramelteon was administered with fluvoxamine: the difference was statistically significant, p=0.001. A 31% increase in the M-II AUC (0-∞), a 60% decrease in M-II C_{max} and a 165% increase in M-II half-life were seen when ramelteon was co-administered with fluvoxamine.

The sponsor concluded that the results of this study confirmed that the CYP1A2 pathway is involved in ramelteon metabolism but that no dose adjustments were needed when ramelteon was co-administered with CYP2C9 inhibitors since the pharmacokinetic changes seen were not

accompanied by a changed incidence of adverse events. The sponsor will advise caution when ramelteon is used together with a CYP1A2 inhibitor.

7.4.2.5.4 Omeprazole

TL036 was a randomized open-label 3-period crossover study to evaluate the effects of a CYP2C19 inhibitor on the multiple-dose pharmacokinetics of ramelteon and its metabolites. Additionally, the study assessed the effect of ramelteon on omeprazole.

Subjects (n=30) were randomized into one of the six treatment sequences. The three treatment groups were 16 mg of ramelteon alone, 40 mg omeprazole alone or ramelteon 16 mg and omeprazole 40 mg dosed daily in three 7-day treatments. After a 5-day washout, the subjects would crossover to another therapy.

In order to evaluate serum concentration of ramelteon as well as plasma concentration of omeprazole, blood was collected 15 minutes before dosing and one hour after dosing on days 1, 5, and 6. Blood was also collected 24 hours after dosing on Day 7.

A 30% decrease in the ramelteon AUC (0-∞) and C_{max} were seen when co-administered with omeprazole.

A 29% increase in the M-II AUC (0-∞), and a 16% increase in M-II C_{max} were seen when ramelteon was co-administered with omeprazole.

There were no differences in the C_{max} or AUC of omperazole after administration in conjunction with ramelteon as compared to omeprazole alone.

The sponsor concluded that the results of this study confirmed that the CYP2C19 pathway is not significantly involved in ramelteon metabolism. While high-dose omeprazole does not inhibit ramelteon metabolism, it does act as a mild inducer of enzyme CYP2C19.

No dose adjustments are needed when ramelteon is co-administered with CYP2C19 inhibitors.

7.4.2.5.5 Rifampin

TL035 was a randomized open-label single-sequence study to evaluate the effects of a CYP inducer on the single-dose pharmacokinetics of ramelteon and its metabolites.

Subjects (n=28) received a single dose of ramelteon 32 mg on day 1 followed by rifampin 600 mg daily on days 3 through 12. No study drug was given on day 2. Single doses of ramelteon 32 mg and rifampin 600 mg were given on day 13.

In order to evaluate serum concentration of ramelteon, blood was collected before dosing and serially for 24 hours after dosing on days 1 and 13. In order to evaluate plasma concentration of rifampin, blood was also collected on days 10, 11, 12 and 13.

An 80% decrease in peak and total exposure was seen after subjects received multiple doses of rifampin.

The sponsor concluded that the results of this study confirmed that the CYP system is significantly involved in ramelteon metabolism.

7.4.2.5.6 Dextromethorphan

TL026 was a randomized open-label 3-period crossover study to evaluate the effects of a dextromethorphan on the single-dose pharmacokinetics of ramelteon and its metabolites. Additionally, the study assessed the effect of ramelteon on the single-dose pharmacokinetics of Dextromethorphan, its major metabolite, dextrophan, and 2 of its minor metabolites, 3 hydroxymorphinan and 3 methoxymorphinan.

Subjects (n=36) were randomized into one of the six treatment sequences. The three treatment groups were 32 mg of ramelteon alone, 30 dextromethorphan alone or ramelteon 32 mg and dextromethorphan 30 mg dosed in three 1-day treatments. After a 7-day washout, the subjects would crossover to another therapy.

In order to evaluate serum concentration of ramelteon and its metabolites as well as plasma concentration of dextromethorphan and its metabolites, blood was collected before dosing and serially for 24 hours after dosing. Urine was also collected before dosing and serially for 24 hours after dosing to measure the concentrations of both drugs.

There were no significant differences in the C_{max} or AUC of ramelteon or M-II after administration in conjunction with dextromethorphan as compared to ramelteon alone.

There were no significant differences in the C_{max} or AUC of dextromethorphan or its metabolites after administration in conjunction with ramelteon as compared to dextromethorphan alone.

The sponsor concluded that ramelteon is not a CYP2D6 isozyme inhibitor nor was there any evidence of an inhibitory effect on the CYP3A4 mediated metabolism of dextrophan to 3-hydroxymorphinan. After this study, the sponsor concluded that no dose adjustments are needed when ramelteon is co-administered with dextromethorphan.

7.4.2.5.7 Theophylline

TL027 was a randomized open-label 2-period crossover study to evaluate the effects of theophylline, a CYP1A2 substrate, on the multiple-dose pharmacokinetics of ramelteon and its metabolites. Additionally, the study assessed the effect of ramelteon on the multiple-dose pharmacokinetics of theophylline.

Subjects (n=36) were randomized into one of the four treatment sequences: 32 mg of ramelteon alone then concomitant administration of ramelteon 32 mg and theophylline 300 mg; theophylline 300 mg alone then concomitant administration of ramelteon 32 mg and theophylline 300 mg; concomitant administration of ramelteon 32 mg and theophylline 300 mg then ramelteon 32 mg alone; concomitant administration of ramelteon 32 mg and theophylline 300

mg then theophylline 300 mg alone. Study medications were dosed daily in two 10-day treatments. A 5-day washout period occurred between the two treatment phases.

In order to evaluate serum concentration of ramelteon as well as plasma concentration of omeprazole, blood was collected before dosing and serially for 72 hours after dosing on day 10.

A 35-40% decrease in the ramelteon AUC (0-∞) and C_{max} was seen when co-administered with theophylline.

A 12% increase in the M-II AUC (0-τ) without any change in M-II C_{max} was seen when ramelteon was co-administered with theophylline.

There were no differences in the C_{max} or AUC of theophylline after administration in conjunction with ramelteon as compared to theophylline alone.

Due to the high intersubject variability seen with ramelteon, the sponsor concluded that no dose adjustments are needed when ramelteon is co-administered with CYP1A2 substrates.

7.4.2.5.8 Fluoxetine

TL034 was a randomized open-label 1-period single-sequence study to evaluate the effects of fluoxetine, which is both a substrate and potent inhibitor of CYP2D6 as well as an inhibitor of CYP2C9, CYP2C19 and CYP3A4, on the single-dose pharmacokinetics of ramelteon and its metabolites.

Subjects (n=28) received a single dose of 16 mg of ramelteon alone on Day 1, followed by fluoxetine 40 mg daily on Days 3 through 12 followed by single doses of ramelteon 16 mg and fluoxetine 40 mg on Day 13.

In order to evaluate serum concentration of ramelteon as well as plasma concentration of fluoxetine, blood was collected before dosing and serially for 24 hours after dosing on day 1 (ramelteon only) and day 13 (both products).

A 50% increase in the ramelteon AUC (0-∞) and a 40% increase in the C_{max} were seen when co-administered with fluoxetine.

A 52% increase in the M-II AUC (0-∞), and a 17% increase in M-II C_{max} were seen when ramelteon was co-administered with fluoxetine.

The sponsor concluded that the results of this study confirmed that fluoxetine does inhibit ramelteon metabolism but that the marked inhibition seen in another study was due to the fluvoxamine related inhibition of CYP1A2 and did not reflect an SSRI class effect.

No dose adjustments are recommended when ramelteon is co-administered with CYP2D6 inhibitors.

7.4.2.5.9 Ethanol

TL028 and TL043 were randomized double-blind 4-period crossover studies to evaluate the potential pharmacodynamic interaction of ramelteon and ethanol. TL028 also evaluated the pharmacokinetic interaction of the drugs.

TL028 enrolled 24 subjects; 22 of whom completed the study. TL043 enrolled 28 subjects and 26 subjects completed the study. Both studies had the following four 1-day treatments, with a 6-day washout, which subjects received in a randomized sequence: 1)ramelteon 32 mg + placebo ethanol, 2) ethanol 0.6 g/kg + placebo ramelteon, 3)ramelteon 32 mg + ethanol 0.6 g/kg, and 4) placebo ramelteon + placebo ethanol.

Blood samples for pharmacokinetic analysis were collected before dosing and serially for 24 hours after dosing in study TL028. Blood samples were collected at one and two hours post-dose in TL 043.

Both studies assessed pharmacodynamic measures of performance and memory using the DSST, PVT, and VAS for alertness. TL028 used the HVLT andTL043 used the DWR.

A 47% increase in the ramelteon AUC (0-∞) and a 43% increase in the C_{max} were seen when ethanol and ramelteon were administered together. No effects on ethanol peak or exposure were detected with co-administration.

Evidence of additive pharmacodynamic effects of the combination was seen in the PVT and the VAS data from study TL028 and the DSST, PVT and VAS data from TL043.

The sponsor concluded that patients should be "advised to use caution" if they use the medications concomitantly.

7.4.2.5.10 Midazolam

TL024 was an open-label single-sequence study to evaluate the effects of multiple doses of ramelteon on the pharmacokinetics of midazolam, a CYP 3A4 substrate, and its major metabolite.

Subjects (n=28) received a single dose of 10 mg of midazolam alone on Day 1, followed by ramelteon 32 mg QD alone on Days 4 through 12 followed by single doses of ramelteon 32 mg and midazolam 10 mg on Day 13. Days 2 and 3 were washout days.

Blood and urine samples were collected before dosing and serially for 48 hours after dosing. Plasma concentration of midazolam and its metabolites was assessed on Days 1 and 13. Plasma concentration of ramelteon and its metabolites was assessed on Day 13.

There were no differences seen when the pharmacokinetics of midazolam administered as a single drug were compared to the pharmacokinetics of midazolam administered in combination with ramelteon.

The sponsor concluded that the results of this study confirmed that ramelteon is neither an inducer nor an inhibitor of the CYP3A4 isoenzyme.

No dose adjustments are recommended when ramelteon is co-administered with CYP3A4 inhibitors.

7.4.2.5.11 Warfarin

TL033 was an open-label single-sequence study to evaluate the effects of multiple doses of ramelteon on the pharmacokinetics of warfarin. The sponsor evaluated the effects on the R-enantiomer (a CYP1A2 substrate) and the S-enantiomer (a CYP2C9 substrate).

Subjects (n=24) received a single loading dose of warfarin on Day -7: men 8 mg; women 6 mg. They received a single dose of warfarin on Day -6: men 4 mg; women 3 mg. Over day -5 to -1, all participants received a daily warfarin dose titrated from 1 to 15 mg to achieve stable PT values with a target range of 1.2 to 1.7 times baseline. Which ever dose provided a stable level was repeated on Day 0. On days 1-7, participants received their individualized warfarin dose and ramelteon 16 mg daily on Days 1 to 7.

Blood samples were collected before dosing and serially for 24 hours after dosing on Days 0 and 7 for analysis of plasma concentrations of warfarin (both enantiomers) and on day 7 for ramelteon concentrations.

There were no significant differences seen when the PT and INR of warfarin administered as a single drug were compared to the PT and INR of warfarin administered in combination with ramelteon.

The sponsor concluded that the results of this study confirmed that ramelteon is neither an inducer nor an inhibitor of the CYP1A2 or the CYP2C9 isoenzymes.

7.4.2.5.12 Digoxin

TL037 was an randomized open-label 2 period crossover study to evaluate the effects of multiple doses of ramelteon on the pharmacokinetics of digoxin, a P-glycoprotein substrate.

Subjects (n=24) received either digoxin alone or digoxin plus ramelteon 16 mg on Days 1-12, then crossed over to the opposite treatment after a 14-day washout. On Day 1, digoxin was dosed at 0.5 mg in the AM followed by 0.25 mg 12 hours later. On Days 2-12, subjects received digoxin 0.2 mg daily.

Blood samples were collected before dosing and serially for 24 hours after dosing for analysis of serum concentrations of digoxin on Days 1 and 8-12. Blood samples were collected before dosing and serially for 24 hours after dosing for analysis of serum ramelteon concentrations on day 12. Urine samples were collected for urinary excretion of digoxin on Days 1 and 12.

Concomitant administration of ramelteon and digoxin reduced peak digoxin exposure by 10% and total exposure by 3%.

Table 49: Ramelteon effects on the pharmacokinetics of Digoxin

	Arithmetic Mean (±SD)		LS Mean		
	Digoxin		Digoxin		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Digoxin AUC(0-τ) (ng·hr/mL)	17.7 (3.87)	16.9 (3.65)	17.2	16.7	96.78 (92.12, 101.68)
Cmax (ng/mL)	2.56 (0.80)	2.35 (0.74)	2.47	2.25	90.83 (79.14, 104.24)
Tmax (hr) (b)	0.50 (0.50, 1.03)	1.00 (0.50, 4.00)	N/A	N/A	N/A
T1/2 (hr)	N/A	N/A	N/A	N/A	N/A

Source: [48].

N=20.

N/A indicates not applicable.

(a) Ratio of the LS means = (digoxin + digoxin/ramelteon alone) ×100.

(b) Tmax = median (minimum, maximum).

(Table 2p from section 2.7.2 summary of clinical pharmacology studies)

The sponsor is not recommending a dose adjustment when ramelteon is used with a P-glycoprotein substrate.

7.4.2.6 Causality Determination

Ramelteon, as demonstrated in the current studies may be considered capable of producing the following adverse effects:

- Somnolence
- Dizziness
- Headache
- Nausea
- Eye pain/Visual disturbance
- Hyperprolactinemia

There are other adverse events which have been reported but the causality is less clear in those cases.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor recommends that adult patients with chronic insomnia take a single eight milligram tablet of ramelteon within 30 minutes of bedtime. During the sleep laboratory components of the development program, ramelteon was administered on the proposed schedule. The pharmacokinetic data demonstrated that the peak levels of ramelteon occurred between 30 minutes and 90 minutes after dosing.

The sponsor notes that while doses of 4 to 64 milligrams were studied and, in their analysis, shown to be efficacious, the 8 milligram dose appeared to give the most consistent results. It is noted that no consistent efficacy dose-response correlation was ascertained during the development program.

When ramelteon 16 mg was administered to fasting healthy adults, an approximately 50-fold difference in C_{max} between minimum and maximum values for a given individual and an 80-fold difference in AUC between minimum and maximum values for a given individual were noted. A two fold difference in AUC was found when elderly subjects were compared with adults; the sponsor concluded that a dose adjustment based upon age was not necessary in light of the wide intersubject variability.

8.2 Drug-Drug Interactions

8.2.1 CYP3A4 inhibitors

No dose adjustments are recommended when ramelteon is concurrently administered with CYP3A4 inhibitors.

8.2.2 CYP2C9 inhibitors

No dose adjustments are recommended when ramelteon is concurrently administered with CYP2C9 inhibitors.

8.2.3 CYP1A2 inhibitors

The sponsor advised caution when ramelteon is used together with a CYP1A2 inhibitor though no specific dose adjustments are advised.

The Agency's review of the submitted material leads us to disagree with this assessment. We will be contraindicating the product for concomitant use with CYP1A2 inhibitors.

8.2.4 CYP2C19 inhibitors

No dose adjustments are needed when ramelteon is co-administered with CYP2C19 inhibitors.

8.2.5 CYP2D6 inhibitors

No dose adjustments are recommended when ramelteon is co-administered with CYP2D6 inhibitors.

8.2.6 Dextromethorphan

No dose adjustments are recommended when ramelteon is co-administered with dextromethorphan.

8.2.7 Theophylline

No dose adjustments are recommended when ramelteon is co-administered with theophylline or other CYP1A2 substrates.

8.2.8 Ethanol

In light of evidence of pharmacodynamic effects of the combination, the sponsor concluded that patients should be "advised to use caution" if they use the medications concomitantly.

8.2.9 Digoxin

Concomitant administration of ramelteon and digoxin reduced peak digoxin exposure by 10% and total exposure by 3%. The sponsor is not recommending a dose adjustment when ramelteon is used with a P-glycoprotein substrate.

8.3 Special Populations

[*Reviewer's note: The safety details for the populations given below were discussed earlier in this review.*]

8.3.1 Gender

There is no consistent evidence that gender has an effect on the safety or efficacy of this product

8.3.2 Age

There is no consistent evidence that age has an effect on the safety or efficacy of this product, however a subgroup analysis of adverse events by age did reveal that the proportion of the elderly who complained of anorexia, depression, and myalgia was higher than that of he non-elderly adults.

8.3.3 Ethnicity

There is no evidence that ethnicity has an effect on the safety or efficacy of this product.

8.3.4 Hepatic impairment

No dose adjustment is proposed by the sponsor for patients with mild to moderate hepatic impairment. Since the product was not studied in patients with severe hepatic impairment, it will not be recommended for use in that population.

The Agency's review of the submitted material leads us to disagree with this assessment. We will be contraindicating the product for use in persons with hepatic impairment.

8.3.5 Renal impairment

The sponsor is not recommending dose adjustment of ramelteon for patients with renal impairment, even those who require chronic hemodialysis.

The Agency's review of the submitted material leads us to disagree with this assessment. We will be recommending that the product be used cautiously in persons with renal impairment.

8.3.6 Chronic obstructive pulmonary disease (COPD)

The sponsor is not recommending dose adjustment of ramelteon for patients with mild to moderate COPD.

8.3.7 Obstructive sleep apnea

The sponsor is not recommending dose adjustment of ramelteon for patients with mild to moderate sleep apnea.

8.4 Pediatrics

This product is not indicated for use in children.

In November 1999, an advisory committee considered the use of hypnotics in children and concluded that there was no clear health benefit from the use of hypnotics in the general pediatric population. The Agency did consider that there might be subsets within the pediatric population for whom hypnotics would be indicated and suggested that PK/PD studies might give important information.

This sponsor has requested a deferral of studies in the pediatric population, in accordance with the Division's recommendation at the pre NDA meeting held on June 22 2004. We will grant the deferral pending postmarketing data from the adult population. If this product does indeed have effect on the endocrine system, use in pubescent children would be a matter of some concern.

8.5 Advisory Committee Meeting

The agency did not convene an advisory committee meeting related to use of this product in the adult population.

8.6 Literature Review

The sponsor performed an extensive literature review and submitted a comprehensive bibliography with this submission.

I read approximately 40% of the articles provided and performed my own literature search specifically focusing on prolactinomas and hyperprolactinemia.

I have listed a few of the more pertinent references in the appendix.

8.7 Postmarketing Risk Management Plan

There is no recommended risk management plan for this product.

8.8 Other Relevant Materials

There are no other relevant materials for this product.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

Insomnia is an interesting disorder as it is one of the few conditions with objective and subjective means of measuring the same endpoint. Both objective and subjective measurements are important for this condition, and the case could be made that from a clinical standpoint, the subjective measures are perhaps more important. Unlike a anti-hypertensive or a cholesterol lowering agent, in which the patient is reliant upon the clinician's assessment of the objective lab data in order to determine efficacy, in this case the patient's subjective determination of effectiveness or lack thereof will not be negated by the fact that there is or isn't objective evidence of efficacy. As we realize that insomnia has both a physiologic and a psychiatric component, it is important that a proposed hypnotic demonstrate objective (e.g. sleep laboratory PSG) and subjective (e.g. outpatient sleep diaries) evidence of efficacy.

Upon the realization that the outpatient study (TL020) in adults had failed to demonstrate efficacy on the primary endpoint, the company proposed the following explanatory hypotheses: the novel mechanism of action of their product makes it difficult to appreciate the shortened LPS and increased total sleep time (TST) provided and the efficacy of ramelteon may be more vulnerable to the effects of poor sleep hygiene than benzodiazepine receptor agonists. While indeed this product may have a subtle mechanism of action that makes it difficulty for the end-user to appreciate its' beneficial effects, that does not relieve the sponsor of the responsibility to effectively demonstrate efficacy with appropriate endpoints.

Safety

There were two deaths reported during this clinical development program: both were patients who were struck by motor vehicles.

There were multiple SAEs reported during development including a woman who was discovered to have a prolactinoma. The labeling for this product will include an instruction to the practitioner to evaluate prolactin levels when clinically appropriate.

The most frequently reported treatment emergent adverse events (TEAE) during this development program were headache, next-day somnolence, nausea and dizziness.

In general, no statistically significant next-day residual effects on objective measures or on subjective measures were seen. In a single study, at 8 mg, a worse delayed recall score and a worse immediate recall score was seen at week 3. In this same study, subjects felt more fatigued at week 1 and more easily irritated/more sluggish at week 3.

Pharmacotoxologic findings
During preclinical development, one of the chromosomal aberration assays was found to be positive. Additionally the rate of hepatic tumors seen in rodent models was higher than might have been expected. Although, even when taken together, these findings in the absence of human correlation do not preclude approval, they do suggest that this product bears careful scrutiny in the first 24-36 months post-approval when it will almost certainly be used in healthy females of child-bearing potential. As the product moves into a wider market, I would suggest that the company set up a pregnancy registry with mandatory reporting incorporated into the annual report to the Agency so that both Takeda and the FDA may be alerted about patients who become pregnant while on medication and any potential adverse events that might arise during those pregnancies.

The possible relationship between this product and neoplasms in rodents is an area of concern. While the rate of neoplasia was very low during this development program, the sample size was small. It would behoove Takeda and the Agency to monitor the post-marketing adverse events for evidence of an increased rate of neoplasms in humans, with hepatic, pituitary and mammary gland tumors being of intense interest. Having said that, it will of course be difficult to tease out potential causality with respect to mammary gland tumors since those are frequently seen even in women who are not taking any medications.

9.2 Recommendation on Regulatory Action

I recommend an approval action for this product.

The sponsor's primary goal was to demonstrate that ramelteon [ ] by decreasing sleep latency using PSG measurement of latency to persistent sleep as well as subjective measures of time to sleep onset. There is objective evidence that this product decreases the latency to persistent sleep for up to 35 days therapy. There is inconsistent subjective evidence that this product does so. I can concur that this product has an immediate hypnotic effect may appropriately be used in the short-term treatment of insomnia.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no recommended risk management activity for this product.

9.3.2 Required Phase 4 Commitments

[ ]

3. A future safety study should be done to obtain additional data on the extent and persistence of the elevated prolactin levels seen in study 032. This study should also collect data on the rate of neoplasms seen in patients who are chronic ramelteon users.
4. The company should set up a pregnancy registry with mandatory reporting incorporated into the annual report to the Agency for the first 24-36 months after product launch.

9.3.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests for this product.

9.3.4 Labeling Review

I made substantive changes to the following sections as may be seen in the appendix:
CLINICAL PHARMACOLOGY

- Pharmacodynamics and mechanism of action
- Pharmacokinetics, specifically regarding food effects and special populations

CLINICAL TRIALS
Studies Pertinent To Safety Concerns For Sleep-Promoting Agents
Special Studies To Evaluate Effects On Endocrine Function
Study to assess cardiovascular safety
INDICATIONS AND USAGE
CONTRAINDICATIONS
WARNINGS
LABORATORY TESTS
ADVERSE REACTIONS

9.4 Comments to Applicant

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7.1

10 APPENDICES

10.1 Discontinuations for non-serious adverse events (all studies)

System Organ Class/ Preferred term	Study	Subject number
Blood and lymphatic system disorders		
Anemia NOS aggravated	TL/022	10216/201745
Eosinophila	TL007	12153/1028
Neutropenia	TL022	10734/222036
Neutropenia aggravated	TL022	10216/201745
Cardiac disorders		
Palpitations	TL022	12814/221496
Palpitations	TL003	11101/1032
Supraventricular extrasystoles	TL022	12657/201781
Ventricular extrasystoles (PVC)	TL003	11101/1032
Ear and labyrinth disorders		
Hyperacusis	TL020	12695/201319
Labyrinthitis NOS	TL027	12569/271003
Sensation of pressure in ear	TL022	10365/201927
Vertigo	TL025	20733/252176
Endocrine disorders		
Acquired hypothyroidism	TL022	12657/201151
Thyroid nodule	TL022	10228/201580
Adrenal insufficiency NOS	TL022	10904/222070
Eye disorders		
Conjunctivitis	TL021	12549/211002
Eye irritation	TL020	12723/201297
Eye pain	TL020	12719/202348
Photophobia	TL020	12695/201319
Vision blurred	TL022	12432/221024
Papilloedema	TL022	12665/221540
General disorders and administration site conditions		
Fatigue	TL020	12719/202348
Fatigue	TL022	10470/170007
Fatigue	TL022	10470/211371
Fatigue	TL022	12065/221073

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
General disorders and administration site conditions, continued		
Fatigue	TL022	12552/170063
Fatigue	TL022	12661/251205
Fatigue	TL022	12710/211010
Fatigue	TL022	12826/221206
Fatigue	TL032	10366/321236
Fatigue	TL022	12646/221175
Fatigue	TL022	12708/221002
Headache	TL034	135001/341020
Lethargy	TL022	12651/222092
Lethargy	TL022	12714/221314
Lethargy	TL025	20738/251507
Pain NOS	TL022	12432/221017
Pyrexia	TL030	301045
Pyrexia	TL043	24266/431018
Weakness	TL020	10153/201653
Feeling abnormal	TL022	12552/170063
Gastrointestinal disorders		
Abdominal distention	TL022	12104/221050
Abdominal pain NOS	TL020	203370/201434
Abdominal pain NOS	TL022	12665/221295
Abdominal pain NOS	TL022	20768/222085
Abdominal pain NOS	TL034	135001/341020
Abdominal pain NOS	TL025	20738/251509
Abdominal pain upper	TL022	12432/221260
Abdominal pain upper	TL022	12861/221156
Constipation	TL040	11400/401051
Diarrhea NOS	TL020	12692/201077
Diarrhea NOS	TL022	12432/221260
Diarrhea NOS	TL022	12710/221284
Diarrhea NOS	TL022	12862/221212
Diarrhea NOS	TL025	20738/251509
Dyspepsia	TL034	135001/341020
Gastric ulcer hemorrhage	TL022	12679/221231
Gastrointestinal upset	TL025	12726/252568
Irritable bowel syndrome	TL022	12863/221047
Loose stools	TL022	12766/251361
Nausea	TL022	10420/221466

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Gastrointestinal disorders		
Nausea	TL020	12692/201077
Nausea	TL008	12153/1022
Nausea	TL020	12813/201262
Nausea	TL020	12815/201725
Nausea	TL022	12104/221050
Nausea	TL022	12550/221559
Nausea	TL022	12714/251083
Nausea	TL022	12720/221514
Nausea	TL022	12766/201329
Nausea	TL025	20733/252176
Nausea	TL034	135001/341020
Nausea	TL020	20374/201423
Nausea	TL022	12682/221463
Nausea	TL025	12694/221497
Tongue disorder NOS	TL022	12432/221024
Vomiting NOS	TL022	10420/221466
Vomiting NOS	TL008	12153/1022
Vomiting NOS	TL020	12653/201865
Vomiting NOS	TL022	12714/251083
Hepatobiliary disorders		
Hyperbilirubinemia	TL021	12724/211349
Infections and infestations		
Influenza	TL025	21194/252898
Periodontitis	TL022	12721/211212
Sinusitis	TL020	12724/201167
Urinary tract infection NOS	TL025	20738/251509
Urinary tract infection NOS	TL040	11400/401051
Varicella	TL021	12549/211002
Pharyngitis streptococcal	TL021	12549/211002
Pneumonia NOS	TL022	12676/222031
Pneumonia NOS	TL022	12699/251865
Immune System disorders		
Type 1 hypersensitivity	TL007	12153/1028

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Injury, poisoning and procedural complications		
Laceration	TL020	10365/201840
Compression fracture	TL022	12699/251865
Investigations		
Alanine aminotransferase increased	TL021	12724/211302
Alanine aminotransferase increased	TL022	12432/221011
Aspartate aminotransferase increased	TL022	12432/221011
Blood alkaline phosphatase increase NOS	TL025	10365/251090
Blood corticotrophin increased	TL032	20646/321145
Blood cortisol decreased	TL022	10365/201027
Blood cortisol decreased	TL022	10823/201726
Blood cortisol decreased	TL022	12432/222038
Blood cortisol decreased	TL022	12719/221331
Blood creatinine increased	TL022	10308/222055
Blood creatinine increased	TL022	20366/221410
Blood lactate dehydrogenase increased	TL022	12432/221011
Blood lactate dehydrogenase increased	TL025	10365/251090
Blood pressure increased	TL020	20732/201526
Blood prolactin increased	TL032	10366/321343
Blood prolactin increased	TL032	20650/321042
Blood testosterone decreased	TL022	12552/170143
Blood testosterone increased	TL032	20650/321042
Body temperature increased	TL021	10912/211027
Blood thyroid stimulating hormone increased	TL022	12711/221490
Blood urea increased	TL022	20366/221410
Blood GGT increased	TL025	10365/251090
Drug screen positive	TL021	10912/211027
Heart rate increased	TL025	20733/252176
Liver function tests abnormal	TL020	10153/201133
Neutrophil count increased	TL022	12721/211110
Neutrophil count increased	TL022	12699/202280
Weight increased	TL022	12655/221015
Weight increased	TL020	12556/201008
White blood cell count increased	TL022	12699/202280
White blood cell count NOS	TL022	12721/211110
Platelet count increased	TL009	12259/1023

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Metabolism and nutrition disorders		
Hypoalbuminemia	TL025	20738/251509
Hypomagnesemia	TL020	12815/201725
Dehydration	TL022	12699/251865
Musculoskeletal and connective tissue disorders		
Arthralgia	TL022	12665/221295
Muscle cramps	TL022	12820/221475
Muscle spasms	TL022	10355/221294
Muscle twitching	TL020	12695/201319
Muscle weakness NOS	TL022	12065/221073
Osteoarthritis	TL020	12556/201811
Rheumatoid arthritis	TL020	12593/201708
Myalgia	TL030	301045
Neoplasms benign, malignant and unspecified		
Polyp NOS	TL022	20768/221491
Prostate cancer NOS	Tl022	10420/222102
Nervous system disorders		
Ageusia	TL022	12432/221024
Balance impaired NOS	TL025	12813/251124
Depression	TL022	12693/201737
Disturbance in attention	TL022	10470/211097
Disturbance in attention	TL022	12812/221071
Dizziness	TL022	10308/201573
Dizziness	TL022	12065/221073
Dizziness	TL022	12552/170063
Dizziness	TL022	12554/221121
Dizziness	TL022	12557/201752
Dizziness	TL022	12591/221036
Dizziness	TL020	12653/201865
Dizziness	TL020	12695/201319
Dizziness	TL025	12695/251574
Dizziness	TL022	12708/221002
Dizziness	TL022	12714/251083
Dizziness	TL022	12720/221514
Dizziness	TL022	12766/201329
Dizziness	TL025	12766/251364

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Nervous system disorders		
Dizziness	TL025	12813/251124
Dizziness	TL034	135001/341020
Dizziness	TL025	20738/251509
Dizziness	TL022	20766/221427
Dizziness	TL022	20775/221312
Dizziness	TL022	20777/221525
Dizziness	TL022	21019/221586
Facial palsy	TL025	12728/251367
Formication	TL022	10365/201028
Headache NOS	TL022	12065/221073
Headache NOS	TL022	12550/221559
Headache NOS	TL022	12654/211057
Headache NOS	TL022	12671/201061
Headache NOS	TL022	12694/221340
Headache NOS	TL020	12813/201262
Headache NOS	TL022	12721/221459
Headache NOS	TL025	12813/251125
Headache NOS	TL020	12910/201529
Headache NOS	TL022	20777/221525
Headache NOS aggravated	TL022	12724/211476
Headache NOS aggravated	TL022	20766/221427
Headache NOS	TL022	12550/222088
Headache NOS	TL022	12665/221540
Headache NOS	TL022	12721/211110
Hemiparesis	TL022	12704/221505
Increased activity	TL022	20766/221442
Jerky movement NOS	TL022	12662/222084
Memory impairment	TL020	12719/202348
Migraine NOS	TL020	12815/201725
Neurological disorder NOS	TL022	12704/221505
Nervousness	TL022	12662/222084
Paresthesia	TL022	12432/221024
Paresthesia	TL020	12723/201297
Paresthesia	TL022	12820/201253
Parosmia	TL020	12723/201297

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Nervous system disorders		
Sedation	TL022	12672/201660
Sedation	TL020	20756/202241
Sedation	TL022	20366/221298
Sleep apnea syndrome	TL022	20775/221488
Somnolence	TL022	10228/201776
Somnolence	TL022	10308/201683
Somnolence	TL022	12104/221119
Somnolence	TL022	12432/221026
Somnolence	TL022	12432/221148
Somnolence	TL022	12556/201920
Somnolence	TL022	12635/201803
Somnolence	TL022	10470/211097
Somnolence	TL022	12655/221323
Somnolence	TL022	12657/201748
Somnolence	TL022	12682/221463
Somnolence	TL025	12682/251147
Somnolence	TL025	12682/251150
Somnolence	TL020	12695/201319
Somnolence	TL032	10366/321236
Somnolence	TL022	10792/251297
Somnolence	TL022	12714/221314
Somnolence	TL025	12725/251039
Somnolence	TL020	12813/201261
Somnolence	TL020	12813/201262
Somnolence	TL032	12927/321025
Somnolence	TL032	20354/321139
Somnolence	TL025	20370/251481
Somnolence	TL020	20374/201423
Somnolence	TL022	20765/221392
Somnolence	TL022	20765/221454
Somnolence	TL022	20766/221506
Somnolence	TL022	20766/221593
Somnolence	TL022	12708/221002
Somnolence	TL022	12646/221175
Syncope	TL020	12723/201297

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Nervous system disorders		
Syncope	TL021	12769/211131
Transient ischemic attack	TL025	12634/251830
Psychiatric disorders		
Affect lability	TL022	12651/221007
Agitation	TL023	12065/231219
Agitation	TL022	12588/221416
Anorgasmia	TL020	20373/201361
Anxiety	TL020	12910/201530
Anxiety	TL022	12552/170063
Anxiety	TL022	12635/251005
Anxiety	TL022	20768/221242
Confusion	TL025	12725/251039
Decreased activity	TL022	20765/221448
Depression	TL022	12699/251865
Depression	TL020	12719/202348
Depression	TL022	12727/221571
Depression	TL022	12826/221053
Depression	TL022	12918/221372
Depression	TL022	12588/221416
Derealisation	TL020	20756/202241
Derealisation	TL025	12695/251574
Hypervigilence	TL022	10355/221302
Insomnia	TL020	12813/201262
Insomnia	TL022	10734/221142
Insomnia exacerbated	TL022	20766/221442
Insomnia	TL022	20766/222126
Insomnia exacerbated	TL020	12723/201297
Insomnia exacerbated	TL020	12723/201299
Insomnia exacerbated	TL022	09843/222047
Insomnia exacerbated	TL022	10365/201028
Insomnia exacerbated	TL022	10365/201925
Insomnia exacerbated	TL022	12827/221411
Insomnia exacerbated	TL022	21017/221511
Insomnia exacerbated	TL022	12863/221090
Insomnia exacerbated	TL025	12695/251574

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Psychiatric disorders, continued		
Insomnia exacerbated	TL025	12695/251574
Insomnia exacerbated	TL025	20381/251437
Insomnia exacerbated	TL025	20381/252201
Insomnia exacerbated	TL025	20741/251588
Insomnia exacerbated	TL022	12588/221416
Irritability	TL022	20765/22170
Mood alteration NOS	TL022	20765/221317
Mood disorder, NOS	TL022	21019/221572
Nightmare	TL022	10470/221035
Nightmare	TL022	12863/221040
Restlessness	TL020	12635/201054
Restlessness	TL025	12635/201054
Restlessness	TL022	12588/201958
Sleep disorder NOS	TL022	12661/221561
Sleep walking	TL025	21121/252682
Somnolence	TL022	20775/221218
Tension	TL022	12671/201061
Thinking abnormal	TL022	12649/201951
Thinking abnormal	TL031	12870/311088
Renal and urinary disorders		
Azotemia	TL020	10153/201133
Calculus renal NOS	TL022	10420/221466
Difficulty in micturition	TL020	12723/201299
Proteinuria	TL022	12651/222002
Renal failure NOS	TL022	12727/221207
Reproductive system and breast disorders		
Amenorrhea NOS	TL032	12932/321106
Erectile dysfunction NOS	TL022	10470/211100
Menorrhagia	TL022	12703/201220
Menstruation irregular	TL022	12703/201220
Priapism	TL022	12671/201061

Table of discontinuations for non-serious adverse events, continued

System Organ Class/ Preferred term	Study	Subject number
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive airways disease	TL025	12703/251152
Cough	TL021	10912/211027
Dyspnea NOS	TL025	12813/251124
Pleurisy	TL008	12153/1017
Emphysema	TL022	10355/222120
Skin and subcutaneous tissue disorders		
Alopecia	TL022	12820/221475
Pruritis NOS	TL020	20756/201465
Pruritis NOS	TL034	135001/341020
Rash erythematous	TL022	10216/201672
Rash generalized	EC002	21238/111
Rash maculo-papular	TL022	12549/221058
Rash NOS	TL022	12651/221326
Rash NOS	TL022	12823/221510
Rash NOS	TL025	20384/251476
Rash NOS	TL022	20766/221541
Sweating increased	TL023	2065/231219
Urticaria NOS	TL022	12679/221303
Social circumstances		
Family stress NOS	TL020	12910/201533
Impaired driving ability	TL025	12725/251039
Surgical and medical procedures		
Central nervous system stimulation NOS	TL025	12714/221314
Vascular disorders		
Hot flushes NOS	TL022	12720/251356
Hot flushes NOS	TL022	12814/221496
Hypotension NOS	TL022	12662/222084
Arterial stenosis NOS	TL022	12708/221251

10.2 Review of Individual Study Reports

10.2.1 Study PNFP-002: A randomized, double-blind, placebo-controlled, single-dose, first night effect, sleep laboratory study of two doses of TAK-375 in healthy adult volunteers.

10.2.1.1 Objective

To evaluate the safety and hypnotic efficacy of TAK-375, in a sleep laboratory, after single dose administration of TAK-375 (16 mg or 64 mg) compared with placebo in subjects naïve to a sleep laboratory environment

10.2.1.2 Study design

A randomized, double-blind, placebo-controlled, single-dose, first night effect model of transient insomnia

10.2.1.3 Study population and procedures

10.2.1.3.1 Study duration

2 days per patient

10.2.1.3.2 Entry criteria

Inclusion criteria

1. Healthy adults between 35 and 60 years old, inclusive
2. Usual total sleep time between 6.5 and 8.5 hours, inclusive
3. Usual sleep latency of no more than 30 minutes
4. Habitual bedtime between 8:30 PM and 12 AM
5. Within 20% of ideal body weight
6. Capable of understanding and complying with the protocol
7. Signed informed consent document at screening

Exclusion criteria

1. Pregnancy or lactation
2. Previous sleep laboratory experience
3. Epworth sleepiness scale of >10
4. Sleep schedule changes required by employment within 3 months preceding Day 1 check-in
5. Jet lag within the past 7 days
6. Participation in a weight-loss program
7. Alteration of exercise program within 30 days preceding Day 1 check-in

8. Physical or psychiatric disorder that may be associated with a sleep disturbance
9. Evidence of a significant illness including neurological, hepatic, renal , endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease
10. Unwillingness to reside in the sleep laboratory during the study period or to cooperate fully with investigator/site personnel
11. Known hypersensitivity to TAK-375 or related compounds including melatonin
12. Clinically important abnormal findings in physical examination, ECG variables or clinical laboratory tests.
13. A positive test for hepatitis panel including HAV antibody (only positive IgM was exclusionary), HBV surface antibody (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody or HCV antibodies
14. History of alcohol abuse within 2 years
15. Clinically significant illness within 30 days preceding Day 1 check-in
16. Use of any prescription medication except menopausal-related hormone replacement therapy or contraceptives) within 14 days or OTC medication within 7 days of Day 1 check-in
17. Intent to use any prescription or OTC medication during the study that could interfere with the evaluation of study medication
18. Evidence of recent alcohol consumption as determined by a breathalyzer test at Day 1 check-in
19. A positive urine drug screen including alcohol at screening or Day 1 check-in
20. Use of tobacco products within 90 days prior to study drug administration. Subjects whose urine drug screens at Day 1 check-in were positive for cotinine were excluded
21. Consumption of caffeine-containing products within 6 hours of study drug administration. Subjects whose urine drug screens at Day 1 check-in were positive for caffeine were excluded. Use of any other investigational drug within 30 days or 5 half-lives, whichever was longer

10.2.1.3.3 Study medications

- TAK-375 16 mg
- TAK-375 64 mg
- Placebo

Prohibited concurrent therapy

The use of caffeine was prohibited for 6 hours prior to study drug administration and through study termination. The use of alcohol was prohibited for 48 hours prior to study drug administration and through study termination. OTC medications were prohibited for 7 days prior to study drug administration and through study termination. Prescription medications, except menopausal-related hormone replacement therapy and oral contraceptives, were prohibited for 14 days prior to study drug administration and through study termination.

Permitted concomitant therapy

All concomitant medications taken during the study were recorded on the CRF. Vitamin and dietary supplements were allowed as long as their use had been stable and regular over an

extended period of time. All calcium supplements were permitted, if they were taken as a dietary supplement, for preventative health or as prophylaxis.

10.2.1.3.4 Study procedures

Subjects were to come for a screening visit between 5 and 21 days prior to Study Day 1. At that visit, they were to provide a complete medical history. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. A practice DSST was to be performed. Subjects were to be told to refrain from alcoholic beverages for 48 hours and caffeine containing beverages for 6 hours prior to Study Day 1. Eligible subjects checked into a sleep laboratory on Day 1 approximately 90 to 120 minutes before their usual bedtime. Urine was to be obtained for drug screening. Subjects were to have ingested a moderate meal prior to entering the sleep laboratory. They were expected to fast from the time of dosing until the completion of the procedures on study day 2.

Each participant was to be assigned a four-digit randomization number. All subjects who had a normal total sleep time between 7.5 and 8.5 hours (inclusive) were to receive ascending consecutive numbers beginning with the lowest number. All subjects who had a normal total sleep time between 6.5 and 7.5 hours were to receive descending consecutive numbers beginning with the highest number.

Study participants were to receive the assigned study medications 30 minutes prior to their usual bedtime and then remain out of bed until 2 minutes before their usual bedtime. The lights were to be turned out at the individual subject's usual bedtime and PSG recording was to be performed over the subsequent 8 hours.

Approximately 45-60 minutes after awakening on Day 2, subjects were to complete the DSST and post-sleep questionnaire. Subsequent to that, an ECG, blood draws, and a physical examination were to be completed. Patients were then to be discharged.

10.2.1.3.5 Efficacy parameters

The primary efficacy parameter was latency to persistent sleep, defined as the elapsed time from the beginning of the PSG recording to the onset of the first 10 minutes of continuous sleep, i.e. the number of epochs from the beginning of the recording to the start of the first of 20 consecutive epochs of sleep divided by 2.

The secondary efficacy parameters were total sleep time, sleep efficiency, awake time after sleep onset of persistent sleep, and percentage of sleep in each sleep stage as determined by PSG recording. Subjective assessments such as time to sleep onset, total sleep time and sleep quality were secondary efficacy variables that were determined by the post-sleep questionnaire.

The tertiary efficacy variables were the number of awakenings as after persistent sleep and the number of awakenings greater than 2 minutes after persistent sleep as measured by PSG as well as the patient's assessment of the ease of falling back to sleep and the subjective number of awakenings.

10.2.1.3.6 Statistical analysis

The intent-to-treat population (ITT) was to be defined as all subjects who were randomized and received at least one dose of study medication. This population was the primary one for analysis of safety, efficacy and residual pharmacological effects. The analyses were to be done on observed data collected at screening, day-1 check-in and day-2 check-out.

In the analysis of the primary efficacy variable, latency to persistent sleep, comparisons of each active treatment arm and placebo were to be made using Dunnett's t-tests and least squares means obtained from a two-way ANOVA with center, treatment and treatment by center interaction as factors. The mixed model procedure (PROC MIXED) with all effects fixed and Type III sums of squares were to be used to generate the ANOVA results.

In the analysis of the secondary and tertiary efficacy variables, comparisons of each active treatment arm and placebo were to be made using Dunnett's t-tests and least squares means obtained from a two-way ANOVA with center, treatment interaction as factors. The mixed model procedure (PROC MIXED) with all effects fixed and Type III sums of squares were to be used to generate the ANOVA results.

Additional subgroup analyses defined by age (≤50, >50), usual sleep time (<7.5 hour, ≥7.5 hours) and customary sleep latency (<20 minutes vs. > 20 minutes) were to be analyzed for latency to persistent sleep as well as digit symbol substitution score using a one-way ANOVA.

10.2.1.3.7 Protocol amendments

<u>25 April 2000 (prior to study initiation)</u>

- The urine drug screening for caffeine and cotinine was to be performed only at Day 1 check-in not at screening.
- Inclusion/Exclusion criteria were clarified
  - Subjects with abnormal laboratory values who were being considered for the study had to be reviewed with the [ ] medical monitor not the Takeda medical monitor
  - Subjects with Hepatitis A were only excluded if IgM was positive
  - Norplant was to be considered an acceptable contraceptive
  - Vitamin preparations and stable doses of calcium supplements were to be considered acceptable for concurrent use
- The protocol clarified that the DSST performed at screening was practice only
- The protocol clarified that one of the tertiary efficacy variables was ease of falling back to sleep
- The protocol clarified the PSG procedures to state that subjects should have all electrodes in place no more than one hour prior to normal bedtime and to minimize subjects' free time before lights out. The central scoring center was to notify both [ ] and the study site in writing to conform that the PSG sample was acceptable. Until then study drug was not to be released. Once the PSG sample was approved, the study site was allowed to perform a PSG on their first subject.

01 August 2000

- Subjects were to be seen for Day 1 check-in no more than 21 days after completing the first screening procedures but no sooner than 5 days after the last screening procedures.
- Clinically significant laboratory values were to be reviewed with the [ ] medical monitor
- Subjects who tested positive for hepatitis B surface antibody were allowed in the study if they had received a Hepatitis B vaccination
- Subjects who tested positive for caffeine on Day 1 check-in were allowed in the study but were to be excluded from the subset analyses.
- PSG efficacy parameter definitions were clarified according to revised PSG definitions as defined in Appendix E of the protocol.
    - LPS had been defined as the number of epochs from lights out to the first of 20 consecutive sleep epochs. The revised definition added a comment that "on occasion classification of an epoch as sleep or wake may not be possible due to movement time lasting for more than 50% of the epoch resulting in an indeterminate epoch. Consecutive epochs of sleep may include and will not be interrupted by indeterminate epochs resulting from movement time.
    - Awakenings after persistent sleep had been defined as the number of times after onset of persistent sleep that there is a wake entry of at least one epoch (30 seconds). The revised definition stated that the wake entry had to be at least two epochs in duration and each entry had to be separated by stage 2, 3, 4 or REM sleep in order to be counted.

10.2.1.3.8 Changes to the planned statistical analysis

- While the protocol had called for centers with fewer than 6 randomized patients to be pooled with geographically adjacent centers, no pooling was done since all centers were able to randomize 6 or more patients.
- A secondary analysis of efficacy and residual pharmacological effects was to be performed on those patients who remained in bed for at least 6 ours and had a negative drug screen at Day 1 check-in. There were only 6 patients in the ITTY population who did not meet this criteria, all of whom had a positive drug screen, so this analysis was not performed
- While the protocol specified that if the normality assumption was not met for sleep latency data, non-parametric methods were to be applied, instead of replacing parametric methods with non-parametric methods, non-parametric methods were applied as a supplementary analysis.
- While the protocol indicated that the statistical significance testing for comparability of treatment groups was to be performed at the 0.05 significance level, two sided, instead the p-values for the analysis were displayed without declaring statistical significance due to multiple comparison concerns.
- Adverse events were coded with a standard MedDRA dictionary instead of using a Takeda modified MedDRA dictionary.
- Instead of the planned presentation of subjects with markedly abnormal laboratory values, a listing of subjects with out of normal range laboratory values was presented.

- Laboratory tests with categorical results were not included in change from baseline and shift table analysis though the lab values were listed for review of individual subjects data.

10.2.1.4 Study results

10.2.1.4.1 Trial characteristics

This study began screening subjects on 09 May 2000. The last patient completed the study on 05 October 2000. A total of 375 patients were enrolled and randomized. Both active drug arms had 126 subjects. The placebo arm had 123 subjects. No patients discontinued from any of the treatment arms.

10.2.1.4.2 Demographics

Table 50: Demographics for study PNFP-002

	Placebo N=123	**TAK-375 16 mg N=126**	**TAK-375 64 mg N=126**
Age (years)			
≤50	96 (78%)	105 (83%)	100 (79%)
>50	27 (22%)	21 (17%)	26 (21%)
Mean (SD)	44 (7.11)	45 (6.55%)	44 (7.01)
Sex			
Male	47 (38%)	44 (35%)	44 (44%)
Female	76 (62%)	21 (65%)	71 (56%)
Ethnicity			
White	103 (84%)	110 (87%)	107 (85%)
Black	15 (12%)	10 (8%)	13 (10%)
Hispanic	2 (2%)	2 (3%)	4 (3%)
Asian	2 (2%)	2 (2%)	1 (1%)
Other	1 (1%)	1 (1%)	1 (1%)

There were no statistically significant differences between the groups in the level of habitual tobacco, alcohol or caffeine use. The Epworth sleepiness scale was used at screening: there were no statistically significant differences seen between the treatment groups (p=0.114). The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, quality of usual sleep and decreased ability to function associated with sleep.

10.2.1.4.3 Protocol violations

The 121 patients who were found to have at least one protocol deviation were spread through the three study arms with 38 patients in the placebo group, 47 patients in the 16-mg group and 36 patients in the 64-mg group.

The most commonly reported violation was a violation of inclusion/exclusion criteria, e.g. patients who were enrolled despite being positive for hepatitis A, B or C. Some of the other violations included:

- One patient in the 64 mg group only took 24 mg of the study drug (subject 1013).
- Two patients were enrolled despite having sleep time that was not between 6.5 and 8.5 hours or usual sleep latency > 30 minutes (subjects 2116, 2346).
- Lights out time differing more than 30 minutes from the usual bedtime
    - Four in the placebo group (subjects 2282, 2326, 2045, 2133)
    - Four in the 16 mg group (subjects 2048, 2107, 2040, 2126)
- Use of prohibited medication
    - Vitamin B12 injection (subject 2365-placebo group)
    - Xalatan (subject 2105-placebo group)
    - Ibuprofen (subjects 1004, 2284-16 mg group; subject 2162-64 mg group)
    - Aspirin (subjects 2067, 2239, 2280-16 mg group)
    - Timoptic (subject 2075-16 mg group)
    - Claritin (subject 2185-16 mg group)
    - Hydrocortisone cream (subject 2036-16 mg group)
    - Peppermint oil (subject 1017-64 mg group)
    - Alka-seltzer plus (subject 2278-64 mg group)
    - Allegra (subject 2164-64 mg group)
    - Acetaminophen (Subject 2372-64 mg group)
    - "Healthcare nonaspirin" (Subject 2310-64 mg group)
    - Hydrocodone (Subject 2063-64 mg group)
    - Topical steroid cream (Subject 2042-64 mg group)

The reported protocol violations did not lead to any study discontinuations.

[*Reviewer's note: The only protocol violations that may have had an impact on efficacy were the eight patients who had lights out differing more than 30 minutes from the usual, and the one patient who used hydrocodone, which may have a sedative effect. Since this study is not being used in support of efficacy for the proposed indication, no re-analysis of the data was done.*]

10.2.1.4.4 Efficacy endpoints

Analyses were performed on the ITT population. The overall treatment effect was tested using ANOVA with effects for treatment and center. Treatment by investigator interaction was to be evaluated at the p=0.10 level for the analysis of the primary efficacy endpoint: latency to persistent sleep. Pairwise comparisons were done using Dunnett's t-test from the ANOVA model of the overall treatment comparison. No evaluation of the per-protocol population was done.

All subjects were to be analyzed in the dose group to which they were randomized. Specific subgroups were to be identified for analysis of latency to persistent sleep and digit–symbol substitution score using a one-way ANOVA. Those subgroups were age (≤50 years vs. > 50 years), usual total sleep time (<7.5 hours vs. ≥7.5 hours) and usual sleep latency (≤ 20 minutes vs. > 20 minutes).

Primary endpoint

Latency to persistent sleep (LPS) measured by polysomnograph (PSG), was defined by the protocol as the time from the beginning of the PSG recording to the onset of the first ten minutes of continuous sleep.

PSG data from five subjects were considered unavailable for analysis.

- Site 0009-data were lost after receipt at the PSG central scoring center
  - Subject 2260 (16 mg)
  - Subject 2257 (64 mg)
  - Subject 2263 (64 mg)
- Site 0010-data were unreadable
  - Subject 2202 (64 mg)
  - Subject 2203 (16 mg)

Analysis of the data from the remaining patients revealed a statistically significant treatment effect for both groups when compared to placebo ($p<0.001$). When evaluated by non-parametric methods, the overall treatment effect and the individual effects remained significant.

Table 51: LPS-ITT population

	Placebo (n=123)	Tak-375 16 mg (n=124)	Tak-375 64 mg (n=123)
LPS (minutes)			
Mean (SD)	24.6 (21.94)	14.1 (15.14)	15.5 (15.43)
Median	19.0	9.8	11.0
LS mean (LSM)	22.6	12.2	13.4
LSM difference from placebo (95% CI)		-10.4 (-15.3, -5.5)	-9.2 (-14.1, -4.3)

(study report table 11.4a)

Secondary endpoints

- Total Sleep Time (TST)

Analysis of the data from the remaining patients revealed a statistically significant treatment effect for both groups when compared to placebo (p=0.008): TAK-357 16-mg group (p=0.007); TAK-375 64-mg group (p=0.033).

Table 52: TST-ITT population study report table 11.4b

	Placebo (n=123)	Tak-375 16 mg (n=124)	Tak-375 64 mg (n=123)
TST (minutes)			
Mean (SD)	411.3 (41.7)	425.4 (37.58)	422.4 (34.81)
Median	421	433.8	427.0
LS mean (LSM)	413.3	427.3	424.7
LSM difference from placebo (95% CI)		14.0 (3.4, 24.6)	11.4 (0.8, 22.1)

- Sleep Efficiency (SE)

Analysis of the data from the remaining patients revealed a statistically significant treatment effect for both groups when compared to placebo (p=0.008): TAK-357 16-mg group (p=0.006); TAK-375 64-mg group (p=0.037).

Table 53: SE-ITT population study report table 11.4c

	Placebo (n=123)	Tak-375 16 mg (n=124)	Tak-375 64 mg (n=123)
SE (%)			
Mean (SD)	86.0 (8.73)	89.0 (7.78)	88.3 (7.18)
Median	87.7	90.4	89.2
LS mean (LSM)	86.4	89.3	88.7
LSM difference from placebo (95% CI)		3.0 (0.7, 5.2)	2.3 (0.1, 4.5)

- Wake time after sleep onset (WASO)

No overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.436) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 16-mg group (p=0.335); TAK-375 64-mg group (p=0.661).

- Subjective sleep latency (sSL)

While a statistically significant treatment effect was seen when active drug was compared to placebo overall (p=0.022) and for the TAK-357 16-mg group (p=0.013), this effect was not seen in the TAK-375 64-mg group (p=0.125).

- Subjective total sleep time (sTST)

No overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.060) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 16-mg group (p=0.034); TAK-375 64-mg group (p=0.310).

- Subjective sleep quality (sSQ)

While a statistically significant treatment effect was seen when active drug was compared to placebo overall (p=0.012), no statistically significant effects were seen when the groups were considered individually: TAK-357 16-mg group (p=0.257); TAK-375 64-mg group (p=0.211).

- % time in each sleep stage

No overall statistically significant treatment effect was seen when active drug was compared to placebo.

Tertiary
The tertiary variables assessed were the objective number of awakenings after sleep onset (NAASO), the objective number of awakenings after sleep onset (NAASO) that were greater than 2 minutes long, the subjective NAASO and the subjective ease of falling asleep after awakening. These variables demonstrated minimal numerical differences and no statistical difference from placebo.

10.2.1.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.1.5 Reviewer's Summary

This study demonstrated a statistically significant difference in objectively measured LPS for both the 16 mg and the 64 mg dose as compared to placebo, which supports the idea that this drug may have an effect on sleep initiation in transient insomnia. The 16 mg group was found to have a statistically significant subjective improvement in sleep latency and total sleep time. An increase in dose from 16 mg to 64 mg does not appear to provide added benefit since the 64 mg group did not report a statistically significant subjective improvement in those measures. Subgroup analysis demonstrated a statistically significant treatment difference in the next-day residual effect as measured by DSST in the patients over 50 years old who had been treated with 64 mg.

It is of interest to note that the subjective sleep quality results for both the 16 mg and the 64mg group did not reflect the expected improvement despite statistically demonstrated improvement in objective LPS, objective TST and subjective SL.

The increase in objectively measured LPS led to both an increase in TST and improved SE. Since the latter measures are a reflection of the change in LPS, it would be misleading to imply that they are separate drug benefits.

10.2.2 Study TL005: An efficacy, safety, and dose response study of TAK-375 in subjects with primary insomnia.

10.2.2.1 Objective

To evaluate the safety, efficacy and dose response of TAK-375 at doses of 4, 8, 16, and 32 mg compared to placebo in subjects with chronic insomnia as defined by the Diagnostic and Statistical Manual of Mental disorders, 4th edition (DSM IV)

10.2.2.2 Study design

A randomized, double-blind, placebo-controlled, 5-period crossover, dose-response efficacy and safety study in patients with primary insomnia.

10.2.2.3 Study population and procedures

10.2.2.3.1 Study duration

Patients had 4 dosing sequences of 3 days each with a 4 to 12 day washout period between periods.

10.2.2.3.2 Entry criteria

Inclusion criteria

1. Healthy adults ≥18 and <65 years old
2. Women of child-bearing potential must have been currently using oral contraceptives and agreed to use, in addition, a barrier method of birth control during the study for the remainder of the cycle after dosing. Females of childbearing potential must have had a negative serum pregnancy test at screening and within 7 days of the first dose of single-blind medication.
3. Chronic insomnia as defined by DSM IV (sSL >30 minutes, sTST less than 6.5 hours/night and daytime complaints associated with disturbed sleep) for at least 3 months
4. A mean latency to persistent sleep of ≥20 minutes on 2 consecutive PSG screening nights with no night less than 15 minutes and had a mean of at least 60 minutes of wake time during the 480 minutes in bed across 2 nights with no night less than 45 minutes
5. Habitual bedtime between 8:30 PM and 12 AM
6. Within 20% of ideal body weight
7. Capable of understanding and complying with the protocol
8. Signed informed consent document at screening

Exclusion criteria

1. Pregnancy or lactation
2. Known hypersensitivity to TAK-375 or related compounds including melatonin

3. Sleep schedule changes required by employment within 3 months preceding Day 1 check-in
4. Had flown across greater than 3 time zones within the past 7 days
5. Participation in a weight-loss program or alteration of exercise routine within 30 days preceding Check-in on Day 1
6. History of psychiatric disorder (including anxiety), seizures, drug addiction, sleep apnea, nocturnal myoclonus and/or mental retardation
7. History of depression within the previous 3 years
8. History of alcohol abuse within past 2 years
9. Clinically significant illness within 30 days preceding Day 1 of study
10. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease
11. Use of St. John's wort or melatonin or consumption of grapefruit or grapefruit juice within 2 weeks of study Day 1
12. One or more nights in a sleep laboratory within 30 days prior to Day 1 of the study
13. Use of tobacco products within 90 days prior to study drug administration.
14. Use of psychotropic drugs within 3 weeks of single blind medication. Subjects taking central nervous system medication must have completed a pre-study washout period of 3 weeks prior to single-blind study medications. The medications in question must not have been used to treat psychiatric diseases.
15. Use of any other investigational drug within 30 days or 5 half-lives, whichever was longer
16. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the two weeks prior to screening.
17. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests (including a fasting blood glucose level > 126 mg/dL) as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
18. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody or HCV antibodies
19. A serum cortisol level > 20 micrograms/dl, then a 24-hour urine free cortisol was determined and if the urine cortisol was > 110 micrograms/24 hours, the subject was excluded
20. A positive urine drug screen including alcohol at screening. Evidence of recent alcohol consumption as determined by a breathalyzer test at Day 1 check-in
21. Apnea-hypopnea index (per hour of sleep) $\geq$10 as seen on the first night of PSG screening
22. Periodic leg movements with arousal index (per hour of sleep) $\geq$10 as seen on the first night of PSG screening
23. Unwillingness to reside in the sleep laboratory during the study period or to cooperate fully with investigator/site personnel

24. Any additional conditions that in the investigator's opinion would either prohibit the subject from completing the study or not be in the best interest of the subject

10.2.2.3.3 Study medications

- TAK-375 4 mg
- TAK375 8 mg
- TAK-375 16 mg
- TAK-375 32 mg
- Placebo

Prohibited concurrent therapy
The use of the following medications was prohibited beginning 2 weeks prior to PSG screening: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, herbal preparations with CNS effects, narcotic analgesics and all beta blockers.

The use of St. John's wort, melatonin, or grapefruit/grapefruit juice was prohibited for the period from 2 weeks prior to screening through the end of study participation. The use of tobacco was prohibited for the period from 90 days prior to screening through the end of study participation.

Use of alcohol/caffeine was prohibited for the 10 hours preceding administration of study drug.

Permitted concomitant therapy
Study participants were to be allowed to use vitamin supplements and calcium supplements as long as use has been stable and regular over an extended period of time.

10.2.2.3.4 Study procedures

Screening
Subjects were to come for an initial screening visit. At that visit, they were to provide a complete medical history. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation which was to include hepatitis screening, a hematology panel, a serum chemistry panel, and urinalysis. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. A Romberg test was to be performed at this visit as well.

Subjects who maintained eligibility through the initial screening were then to be evaluated by PSG.

During the PSG screening, which lasted two nights, subjects were to practice the visual analog scale (VAS) with questions regarding mood, digit symbol substitution test (DSST) and memory recall tests twice nightly as well as completing the pre-sleep questionnaire nightly. On both nights they were to receive single-blind study medication 30 minutes before their usual bedtime, and PSG was then to be performed for 8 hours. After 8 hours the PSG was stopped and the

subject was awakened if necessary to perform the VAS, DSST and memory recall tests as well as to complete the post-sleep questionnaire. A Romberg test was to be done: if it was positive, it was to be repeated every 15 minutes until negative. Subjects were allowed to leave the study site on the morning of screening study day 2 and asked to return that evening for a repeat night of testing.

Crossover treatment period

This period was comprised of 5 crossover sessions, each of which lasted two nights. Subjects would arrive 2-2.5 hours prior to their usual bedtime for Day 1 assessments, which included vital signs, urine drug screen, breathalyzer test for alcohol, urine pregnancy tests, pre-sleep questionnaire, VAS, DSST and memory recall tests. On both nights they were to receive double-blind study medication 30 minutes before their usual bedtime, and PSG was then to be performed for 8 hours. After 8 hours the PSG was stopped and the subject was awakened if necessary to perform the VAS, DSST and memory recall tests as well as to complete the post-sleep questionnaire. A Romberg test was to be done: if it was positive, it was to be repeated every 15 minutes until negative. Subjects were allowed to leave the study site on the morning of study day 2 and asked to return that evening for a repeat night of testing. After each treatment period, subjects underwent a 5 to 12 day washout period before proceeding to the next trial.

10.2.2.3.5 Efficacy parameters

The primary efficacy variable was latency to persistent sleep.

The secondary efficacy variables were total sleep time, sleep efficiency, awake time after persistent sleep and percentage of time in each sleep stage. Additional subjective secondary variables included time to sleep onset, total sleep time and sleep quality.

The exploratory objective variables included number of awakenings after persistent sleep and number of awakenings greater than 2 minutes after persistent sleep. The exploratory subjective variables included number of awakenings and ease of falling back to sleep.

10.2.2.3.6 Statistical analysis

The intent-to-treat (ITT) population was defined as all subjects who were randomized and received at least one dose of double-blind study medication. The ITT population was to be analyzed for efficacy and safety.

Log transformation of the parameters would be applied for the primary efficacy variable, if the normality assumption for applying the ANOVA analysis was not met and the log-transformation was felt to be appropriate. If non-parametric approaches were used, the Kruskal-Wallis test was to be used to test the overall treatment of differences and the pairwise comparisons between each treatment arm and placebo.

Interactions such as treatment by age and gender would be investigated and formally evaluated only for the analysis of latency to persistent sleep. Those tests would be done at the 0.10 significance level.

10.2.2.3.7 Protocol amendments

The first was dated 31 July 2001 (prior to subject randomization) and contained the following changes:

- Chronic insomnia was further defined as "primary chronic insomnia as defined by the DSM-IV"
- The Washout period was changed from 4-12 days to 5 or 12 days in order to clarify that patients were expected to return on the same day of the week for each visit.
- Clarification of the intent that PSG screening should occur on consecutive nights
- Deleted prior sleep lab experience from the exclusion criteria provided that the subject did not receive investigational drug product.
- Clarified that the use of tobacco products within 90 days of single-blind study medication was a cause for exclusion
- Clarified that use of St. John's wort, melatonin or grapefruit juice within 3 weeks of single-blind medication was a reason for exclusion
- Increased the acceptable levels of cortisol from >20 µg/dL to >30 µg/dL (blood) and from >110 µg/dL to >140 µg/dL (urine).
- The period of withdrawal from prohibited medications was lengthened from 2 weeks to 3 weeks.
- The wording in the reason for discontinuation section was modified to make it consistent with the CRF.
- Added clarification that efficacy parameters were only to be done on the morning of Day 3
- The target difference of 12 minutes in LPS was clarified

The second amendment, dated 08 October 2001, contained the following significant changes as well as minor grammatical corrections:

- Clarified that memory recall tests were to be practiced once nightly during screening
- Defined acceptable methods of birth control in the protocol and in the sample informed consent
- Deleted depression from the exclusion criteria that summarizes psychiatric disorders
- Added depression within the previous 3 years as a separate exclusion criterion
- Clarified the number of tablets administered on each day
- Clarified that VAS and DSST were to be practiced twice at screening
- Added the elbow breadth values where missing on the ideal weights table
- Added a seventh category to the VAS feeling scale that would not be scored

10.2.2.3.8 Study report amendments

There was one amendment made on 08 April 2004. This amendment made the following significant changes in addition to minor spelling changes:

- Clarified the TAK-375 matching placebo lot which had been used for the study
- Provided a list of investigators as well as their corresponding site numbers
- Added text to the protocol deviations section
- Corrected the triglyceride laboratory data conversion factor

The conversion factor used for table 14.3.4.1 was 0.167 which gave a markedly abnormal range of >66.80 mmol/L. The conversion factor should have been 0.0113 which would give a markedly abnormal range of >4.52 mmol/L. The two patients who had abnormal screening levels (using the corrected conversion factor) were noted.

10.2.2.3.9 Changes to planned statistical analysis

Two changes were made:

- Center effect was removed from all analyses
- An auto-regressive covariance structure for the random errors was used in the ANOVA models.

10.2.2.4 Study results

10.2.2.4.1 Trial characteristics

This study began screening subjects on 17 September 2001. The last patient completed the study on 26 February 2002. All 13 participating study centers were in the United States of America.

The sponsor planned to enroll 100 subjects. A total of 107 patients were enrolled and randomized into one of ten treatment sequences but one participant (34010/2022) was excluded from all analyses since she received the wrong treatment.

Two subjects (34008/2027---34001/2052 and 34008/2030----34001/2060) were enrolled in the study twice, completing treatment each time. The sponsor elected to use demographic information from their first participation (34008) only but incorporated all of their available lab data treating them as 4 distinct subjects.

10.2.2.4.2 Demographics

Table 54: Demographics

Age (years)	
Mean (SD)	37.7 (12.16)
Range	18-63
Sex	
Male	38 (35.8%)
Female	68 (64.2%)
Ethnicity	
White	58 (54.7%)
Black	23 (21.7%)
Hispanic	24 (22.6%)
Asian	1 (<1%)
Other	0

There were no statistically significant differences between the groups in the level of habitual tobacco, alcohol or caffeine use. The sleep history for each participant was taken at screening

with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, quality of usual sleep and decreased ability to function associated with sleep. There were no significant differences between the treatment groups when the use of concomitant medications was reviewed.

Four subjects discontinued prematurely.

- Subject 34014/1024 assigned to treatment sequence IV discontinued due to "other", specifically difficulty adhering to the PSG schedule
- Subject 34017/2015 assigned to treatment sequence VII discontinued due to a protocol deviation on study day 2 of period I (TAK-375 16 mg) after receiving 2 doses of TAK-375 16 mg
- Subject 34010/1039 assigned to treatment sequence VII withdrew consent on study day 1 of period I (TAK-375 16 mg) after receiving 1dose of TAK-375 16 mg
- Subject 34010/2022 did not receive treatment as specified by her treatment sequence and was discontinued from the study on study day 9 of period II (TAK-375 8 mg) after receiving 2 doses of TAK-375 16 mg and 2 doses of TAK-375 8 mg

10.2.2.4.3 Protocol violations

Two patients were removed from the study due to protocol violations. Subject 34010/2022 for the reason described above. Subject 34017/2015 was discontinued because of participation in a weight-loss program/alteration of exercise routine within 30 days prior to Day 1 check-in.

10.2.2.4.4 Efficacy endpoints

Primary endpoint

Latency to persistent sleep (LPS) measured by polysomnograph (PSG), was defined by the protocol as the time from the beginning of the PSG recording to the onset of the first ten minutes of continuous sleep. A statistically significant treatment effect for active drug was seen when active drug at all four doses was compared to placebo (p=0.001).

Table 55: LPS-ITT population

	Placebo (PBO) (n=103)	**TAK-375 4 mg (n=103)**	**TAK-375 8 mg (n=103)**	**TAK-375 16 mg (n=106)**	**TAK-375 32 mg (n=103)**
LPS (minutes)					
Mean (SD) **LS mean (LSM)** **LSM-PBO**	38.1 (35.36) 37.7	24.5 (21.58) 24.0 -13.7	24.6 (21.67) 24.3 -13.4	24.2 (22.25) 24.0 -13.7	23.2 (22.5) 22.9 -14.8
p-values for comparison	Overall	4 mg vs. PBO	8 mg vs. PBO	16 mg vs. PBO	32 mg vs. PBO
p-values	<0.001	<0.001	<0.001	<0.001	<0.001

(study report table 11a)

The sponsor performed confirmatory analyses using the log scale and non-parametric analyses. The results from the latter analyses were consistent with the primary analysis.

Secondary Endpoints

- Total Sleep Time (TST)

A statistically significant treatment effect for active drug was seen when active drug was compared to placebo (p=0.001).

Table 56: TST-ITT population study report table 11b

	Placebo (PBO) (n=103)	**TAK-375 4 mg (n=103)**	**TAK-375 8 mg (n=103)**	**TAK-375 16 mg (n=106)**	**TAK-375 32 mg (n=103)**
TST (minutes)					
Mean (SD) **Median** **LS mean (LSM)**	399.9 (49.6) 411.3 400.2	410.0 (47.8) 421.8 411.0	411.8 (45.8) 420.8 412.9	410.9 (42.2) 418.4 411.2	417.1 (43.05) 430.3 418.2
p-values for comparison	Overall	4 mg vs. PBO	8 mg vs. PBO	16 mg vs. PBO	32 mg vs. PBO
p-values	0.001	0.038	0.010	0.032	<0.001

- Wake time after sleep onset (WASO)

No statistically significant treatment effect was seen when active drug was compared to TAK-375 4mg (p=0.757), TAK-375 8 mg (p=0.978), TAK-375 16-mg group (p=0.84) or TAK-375 64-mg group (p=0.887). The mean WASO for the placebo group was 45.8 minutes. In the active groups, the WASO ranged from a high of 49.4 minutes (4 mg group) to a low of 43.4 minutes (32 mg group). Review of the four active treatment groups did not reveal a dose-response effect.

- Percentage of time in REM sleep and stage 1, 2 and 3/4 NREM sleep

The TAK-375 4 mg group was the only one to show a statistically significant increase in total stage 2 sleep time (p=0.021). Each of the treatments studied showed a statistically significant increase in total sleep time in NREM stage 3/4 sleep when compared to placebo. There were no other significant differences from placebo in the amount of NREM stage 1, 2 or REM sleep.

- Latency to REM

No statistically significant treatment effect was seen when active drug was compared to TAK-375 4mg (p=1.0), TAK-375 8 mg (p=0.586) TAK-375 16-mg group (p=0.979) or TAK-375 64-mg group (p=1.0).

- Subjective sleep latency (sSL)

The TAK-375 16 mg group was the only one to show a statistically significant decrease in subjective sleep latency (p=0.015).

- Subjective total sleep time (sTST) and subjective sleep quality (sSQ)

No overall statistically significant treatment effect was seen when active drug at any dose was compared to placebo.

- Sleep Efficiency (SE)

A statistically significant treatment effect in favor of active drug treatment was seen when placebo was compared to TAK-375 4mg (p=0.034), TAK-375 8 mg (p=0.010), TAK-375 16-mg group (p=0.032) or TAK-375 64-mg group (p<0.001).

Table 57: SE-ITT population

	Placebo (PBO) (n=103)	**TAK-375 4 mg (n=103)**	**TAK-375 8 mg (n=103)**	**TAK-375 16 mg (n=106)**	**TAK-375 32 mg (n=103)**
SE					
Mean (SD)	83.3 (10.33)	85.5 (9.97)	85.8 (9.54)	85.6 (9.54)	86.9 (8.96)
Median	85.7	87.9	87.7	87.2	89.6
LS mean (LSM)	83.4	85.7	86.0	85.7	87.1
p-values for comparison	Overall	4 mg vs. PBO	8 mg vs. PBO	16 mg vs. PBO	32 mg vs. PBO
p-values	0.001	0.034	0.010	0.032	<0.001

study report table 11c

Exploratory

Table 58: results from exploratory efficacy variables

(LS Means) Variable	**Placebo** (N=103)	**TAK-375 4 mg** (N=103)	**TAK-375 8 mg** (N=103)	**TAK-375 16 mg** (N=106)	**TAK-375 32 mg** (N=103)
# Awakenings after persistent sleep					
	6.3	7.0	7.0	7.0	7.1*
No. of Awakenings > 2 Minutes after onset of persistent sleep					
	2.0	2.3	2.3	2.5*	2.3
Subjective Number of Awakenings					
	3.2	3.1	3.0	3.1	3.2
Subjective Ease of Falling Back to Sleep Yes (%)					
Day 2 (AM)	48.4	47.7	45.8	48.0	40.2
Day 3 (AM)	45.7	50.0	37.2	46.9	45.7

Modified study report table 11.j

10.2.2.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.2.5 Reviewer's Summary

This study demonstrated a statistically significant difference in objectively measured LPS for all doses studied (4mg, 8 mg, 16 mg, 32 mg) in comparison to placebo, which supports the idea that this drug may have an effect on sleep initiation.

The only group to perceive an improvement in subjective sleep latency was the group who received 16 mg. It is of interest to note that the subjective sleep quality and subjective total sleep time results for the active treatment groups did not reflect the expected improvement despite statistically demonstrated improvement in objective LPS and objective TST.

The increase in objectively measured LPS led to both an increase in TST and improved SE. Since the latter measures are a reflection of the change in LPS, it would be misleading to imply that they are separate drug benefits.

10.2.3 Study TL017: A phase III, randomized, double-blind, placebo-controlled, crossover study to determine the safety and efficacy of TAK-375 in elderly subjects with chronic insomnia

10.2.3.1 Objectives

To evaluate the safety and efficacy of TAK-375 at doses of 4 mg and 8 mg compared to placebo in elderly patients with chronic insomnia.

10.2.3.2 Study design

A randomized, double-blind, placebo-controlled cross-over Phase III study in elderly patients with chronic insomnia

10.2.3.3 Study population and procedures

10.2.3.3.1 Study duration

Patients had 3 dosing sequences of 3 days each with a 5 to 12 day washout period between periods.

10.2.3.3.2 Entry criteria

Inclusion criteria

1. Healthy adults 65 years old or older
2. Chronic insomnia as defined by DSM IV (sSL ≥30 minutes, sTST less than 6.5 hours/night and daytime complaints associated with disturbed sleep) for at least 3 months
3. A mean latency to persistent sleep of ≥20 minutes on 2 consecutive PSG screening nights with no night less than 15 minutes as well as a mean of at least 60 minutes of wake time during the 480 minutes in bed across 2 nights with no night less than 45 minutes
4. Habitual bedtime between 8:30 PM and 12 AM
5. Body Mass Index between 18 and 34, inclusive
6. Capable of understanding and complying with the protocol
7. Signed informed consent document at screening
8. Fluent in English language (reading, writing, speaking)

Exclusion criteria

1. Known hypersensitivity to TAK-375 or related compounds including melatonin
2. Previous participation in a study involving TAK-375
3. Use of any other investigational drug within 30 days or 5 half-lives, whichever was longer, prior to Day 1 of single-blind study medication
4. Sleep schedule changes required by employment within 3 months preceding Day 1 check-in
5. Had flown across greater than 3 time zones within the past 7 days

6. Participation in a weight-loss program or alteration of exercise routine within 30 days preceding Check-in on Day 1
7. History of schizophrenia, bipolar disorder, seizures, sleep apnea, COPD and/or mental retardation or cognitive disorder
8. History of psychiatric disorder, including anxiety or depression, within the previous 12 months
9. History of drug addiction or drug abuse within the past 12 months
10. History of alcohol abuse within past 12 months, as defined in DSM-IV-TR and/or regularly consumes 4 or more alcoholic drinks/day.
11. Clinically significant illness within 30 days preceding Day 1 of study
12. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease, unless controlled and stable with protocol-allowed medication 30 days prior to Day 1 of the single-blind study medication.
13. Use of St. John's wort, melatonin or consumption of grapefruit or grapefruit juice within 2 weeks of study Day 1
14. Use of a central nervous system-active medication within 3 weeks (or 5 drug half-lives whichever is longer) prior to Day 1 of single-blind study medication. These medications must not have been used to treat psychiatric disease.
15. Intent to use any disallowed, prescription or OTC medication during the study that is known to affect sleep/wake function or could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the three weeks prior to screening.
16. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory findings as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator.
17. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBsAg, HBV surface antigen, anti-HBc or anti-HCV
18. Use of tobacco products within 90 days prior to study drug administration
19. One or more nights in a sleep laboratory within 30 days prior to Day 1 of the study
20. A positive urine drug screen including alcohol at screening. Evidence of recent alcohol consumption as determined by a breathalyzer test at Day 1 check-in
21. Apnea-hypopnea index (per hour of sleep) $\geq$15 as seen on the first night of PSG screening
22. Periodic leg movements with arousal index (per hour of sleep) $\geq$20 as seen on the first night of PSG screening
23. Any additional conditions that in the investigator's opinion would either prohibit the subject from completing the study or not be in the best interest of the subject

10.2.3.3.3 Study medications

- TAK-375 4 mg
- TAK-375 8 mg
- Placebo

Prohibited concurrent therapy
Medications prohibited within 3 weeks prior to Day 1 of single-blind treatment and throughout the study included anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H_1 antihistamines, systemic steroids, respiratory stimulants and decongestants, OTC and prescription stimulants, OTC and prescription diet aids, CNS active drugs (including herbal preparations), narcotic analgesics and all beta blockers, St. John's wort, kava-kava, ginko biloba, any other supplements, OTC or prescription medications that may interfere with the evaluation of the study medication.

Other substances that were prohibited within 5 days prior to Day 1 of single-blind study medication and during the study included melatonin or other drugs/supplements known to affect sleep/wake function and grapefruit (solid/juice).

Use of alcohol and caffeine will be prohibited for 10 hours before any and all doses of single-blind and double-blind study medication.

10.2.3.3.4 Study procedures

Screening
Subjects were to come for an initial screening visit. At that visit, they were to provide a complete medical history. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation which was to include hepatitis screening, a hematology panel, a serum chemistry panel, and urinalysis. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. A Romberg test was to be performed at this visit as well.

Subjects who maintained eligibility through the initial screening were then to be evaluated by PSG.

During the PSG screening, which lasted two nights, subjects were to practice the visual analog scale (VAS) with questions regarding mood, digit symbol substitution test (DSST) and memory recall tests twice nightly as well as completing the pre-sleep questionnaire nightly. On both nights they were to receive single-blind study medication 30 minutes before their usual bedtime, and PSG was then to be performed for 8 hours. After 8 hours the PSG was stopped and the subject was awakened if necessary to perform the VAS, DSST and memory recall tests as well as to complete the post-sleep questionnaire. A Romberg test was to be done: if it was positive, it was to be repeated every 15 minutes until negative. Subjects were allowed to leave the study site on the morning of screening study day 2 and asked to return that evening for a repeat night of testing.

Crossover treatment period
This period was comprised of 3 crossover sessions, each of which lasted two nights. Subjects would arrive 2-2.5 hours prior to their usual bedtime for Day 1 assessments, which included vital signs, urine drug screen, breathalyzer test for alcohol, urine pregnancy tests, pre-sleep questionnaire, VAS, DSST and memory recall tests. On both nights they were to receive double-blind study medication 30 minutes before their usual bedtime, and PSG was then to be performed

for 8 hours. After 8 hours the PSG was stopped and the subject was awakened if necessary to perform the VAS, DSST and memory recall tests as well as to complete the post-sleep questionnaire. A Romberg test was to be done: if it was positive, it was to be repeated every 15 minutes until negative. Subjects were allowed to leave the study site on the morning of study day 2 and asked to return that evening for a repeat night of testing. After each treatment period, subjects underwent a 5 to 12 day washout period before proceeding to the next trial.

Electrocardiograms were to be performed on Day 3 of crossover period 2 and at the final visit.

Treatment sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
I	Placebo	8 mg	4 mg
II	4 mg	Placebo	8 mg
III	8 mg	4 mg	Placebo
IV	4 mg	8 mg	Placebo
V	8 mg	Placebo	4 mg
VI	Placebo	4 mg	8 mg

(Table 10a from final study report)

10.2.3.3.5 Efficacy parameters

The primary efficacy variable was mean latency to persistent sleep from nights 1 and 2 of each treatment period.

The secondary efficacy variables were total sleep time, sleep efficiency, awake time after persistent sleep, number of awakenings after persistent sleep and percentage of time in each sleep stage. Additional subjective secondary variables included time to sleep onset, total sleep time, restorative nature of sleep, time awake, number of awakenings and ease of falling back to sleep and sleep quality.

10.2.3.3.6 Statistical analysis

The intent-to-treat (ITT) population was defined as all subjects who were randomized and received at least one dose of double-blind study medication. The ITT population was to be analyzed for efficacy and safety. Analysis for a given variable was only to include patients who had a value for that variable. If a patient were to receive an incorrect study medication, that subject would be removed from the analysis. The efficacy and safety analyses would be based upon the observed data.

The mean of the observations from the two nights of treatment would provide the data fro analysis of the primary and secondary efficacy variables, residual pharmacological variables and special safety variables.

All comparisons between the treatment groups were to be made using t-tests and least squares means and standard errors obtained from the following ANOVA model:

Parameter = seq+ subject (seq) + period +treatment + carryover

The treatment comparisons were to be made at the 0.05 significance level adjusted for two comparisons versus placebo using a stepwise testing procedure.

The efficacy of TAK-35 was to be assessed using Fisher's protected least significant difference (LSD) testing procedure to control the Type I error. The carryover effect was to be evaluated for the primary efficacy variable only. The carryover effect was to be removed from the analysis model for the primary efficacy variable if it was not found to be significant at the 0.100 level.

Important secondary efficacy variables were to be analyzed with a continuation of Fisher's protected LSD procedure. Analysis of total sleep time was to be contingent on observing significance from the F-test of latency to persistent sleep. It the overall F-test of total sleep time was found to be significant, then the analysis of subjective sleep quality was to be performed.

10.2.3.3.7 Protocol amendments

The first amendment protocol was dated 19 August 2002. In this amendment, the sponsor added preliminary results from the 24-month rodent carcinogenicity studies: apparent dose-related increase in hepatic tumors, apparent increased incidence of Hardarian gland adenomas, apparent increase in Leydig cell tumors seen in male rats.

The first amendment protocol was dated 22 November 2002. In this amendment, the sponsor made a few minor administrative changes to the titles of [redacted] The sponsor made the following changes to the statistical analysis plan:

- The subjective restorative nature of sleep was removed from the list of secondary variables.
- The stepwise testing procedure was changed to Fisher's protected LSD testing procedure
- The analyses for the secondary efficacy variables were changed to incorporate the Fisher's protected SD testing procedure as a continuation of the primary analysis.
- Pooled center was removed as a planned factor in the analysis

The sponsor also clarified some definitions of PSG parameters and added a definition for awake time after persistent sleep, specifically "the number of wake minutes from the last sleep minute to the end of the recording."

There was one correction to the clinical study report, dated 20 August 2004. The sponsor reports that the ECG results for subjects 170058 and 170059 [redacted] had been inadvertently recorded on the opposite CRFs. The final visit ECG for patient 170058 should have been recorded as normal, instead of abnormal due to premature atrial contractions. The final visit ECG for patient 170059 should have been recorded as abnormal due to premature atrial contractions instead of normal. The sponsor felt that this correction did not affect the primary or secondary safety and efficacy endpoints so the database was not modified.

[*Reviewer's note: I agree that the change to the clinical study report would not affect the safety finding since the number of patients with premature atrial contractions is overall unchanged.*]

10.2.3.4 Study results

10.2.3.4.1 Trial characteristics

This study began on 21 October 2002 and ended on 9 July 2003. A total of 17 study sites, all of which were in the United States of America, enrolled patients.

All 100 patients who enrolled completed the study. There were no early discontinuations.

10.2.3.4.2 Demographics

Table 59: Demographics for study TL-375-017

	Overall N=100
Age (years)	
Mean (SD)	70.7 (4.63)
Sex	
Male	37 (37%)
Female	63 (63%)
Ethnicity	
White	95 (95%)
Hispanic	4 (4%)
Asian	1 (1%)

(Study report table 10b)

All 100 patients who enrolled completed the study. There were no early discontinuations.

There were no statistically significant differences between the treatment sequences in the level of habitual tobacco, alcohol or caffeine use. The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic. There were no significant differences between the treatment groups when the use of concomitant medications was reviewed. The majority of the participants (87%) were using concomitant medications, such as vitamins (39%), antithrombotic agents (26%), serum lipid reducing agents (25%), anti-imflammatory and antirheumatic agents (24%) and mineral supplements (23%).

10.2.3.4.3 Protocol violations

While breathalyzer tests were negative in all cases where available, the following subjects were found to have positive urine drug screens:
Initial screening:

- 170125 (site 12690): Oxazepam and temazepam
- 170153 (site 12074): Hydrocodone
- 170154 (site 12074): Ethanol

During the single-blind PSG screening:

- 170041 (site 12544): Ethanol
- 170066 (site 12552): Morphine
- 170091 (site 12076): Cotinine

During the double-blind study period

- 170005 (site 12074): Morphine, on Day 1 placebo
- 170006 (site 12074): Norproxyphene, propoxyphene , both on Day 1 placebo
- 170041 (site 12544): Ethanol and morphine on Day 1 placebo
- 170051 (site 12556): Hydrocodone, on Day 1 placebo
- 170091 (site 12076): Cotinine, on Day 1 8 mg
- 170103 (site 12074): Flurazepam, on Day 1 8 mg
- 170160 (site 12552): Ethanol, on Day 1 4 mg

The one reported study medication deviation (subject 10908) was a time delay in dosing of study medication due to staff error. One patient (12544-treatment sequence 6) received a prohibited medication, specifically imipramine.

Twenty-six patients failed to meet the inclusion criteria which stated that they should have a mean sleep latency of 20 minutes or greater per night of screening PSG and a mean of 60 minutes of wake time per night of screening PSG.

[*Reviewer's note: The drugs detected during the initial screening phase would not be likely to affect the efficacy outcome. The drugs detected during the single-blind phase might affect the efficacy outcome: morphine and ethanol may shorten sleep latency; cotinine may prolong sleep latency. The drugs detected during the double-blind phase might affect the efficacy outcome: hydrocodone, propoxyphene, norpropoxyphene, flurazepam, morphine and ethanol may shorten sleep latency; cotinine may prolong sleep latency.*]

10.2.3.4.4 Efficacy endpoints

All 100 subjects were included in the ITT population, which was the primary population for efficacy analyses; 33 subjects were excluded from the PP population.

Primary endpoint

A statistically significant treatment effect in favor of active drug was seen when active drug was compared to placebo ($p<0.001$). This effect was also seen when the PP population was evaluated ($p=0.004$).

Table 60: LPS (minutes)-ITT population

	Placebo (PBO) (n=100)	**TAK-375 4 mg (n=100)**	**TAK-375 8 mg (n=100)**
LS mean (SE) **LSM-PBO (SE)** **95% CI for difference**	38.4 (2.49)	28.7 (2.49) -9.7 (2.64) (-14.9, -4.5)	30.8 (2.52) -7.6 (2.68) (-12.9, -2.3)
Pairwise p-values		<0.001	0.005

(study report table 11a)

Secondary Endpoints

- Total Sleep Time (TST)

A statistically significant treatment effect in favor of active drug was seen when active drug was compared to placebo (p=0.018). This effect was also seen for both the 4mg (p=0.035) and the 8 mg (p=0.01) groups when the PP population was evaluated.

Table 61: TST (minutes)-ITT population

	Placebo (PBO) (n=100)	**TAK-375 4 mg (n=100)**	**TAK-375 8 mg (n=100)**
TST (minutes)			
LS mean (SE)	350.4 (5.04)	359.4 (5.06)	362.0 (5.03)
LSM-PBO (SE)		9.0 (4.26)	11.5 (4.22)
95% CI for difference		(0.6, 17.4)	(3.2, 19.9)
Pairwise p-values		0.036	0.007

(study report table 11b)

- Wake time after sleep onset (WASO)

No statistically significant treatment effect was seen when TAK-375 4mg (p=0.874) or TAK-375 8 mg (p=0.204) was compared to placebo.

- Sleep Efficiency (SE)

A statistically significant treatment effect for active drug was seen when placebo was compared to TAK-375 4mg (p=0.037), or TAK-375 8 mg (p=0.007).

- Number of awakenings after sleep onset

While the number of awakenings seen after use of 8 mg were statistically the same as those seen after placebo (0.016), there was a statistically significant increase in awakenings seen after use of 4 mg (p=0.08).

- Subjective sleep latency (sSL)

The TAK-375 4 mg group was the only one to show a statistically significant decrease in subjective sleep latency (p=0.037).

- Subjective total sleep time (sTST) and subjective sleep quality (sSQ)

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo. An evaluation of the PP population for sSQ did not reveal any treatment difference.

- Subjective wake time after sleep onset (sWASO), subjective ease of falling back to sleep and subjective Number of Awakenings after sleep onset (sNAW)

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo.

10.2.3.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.3.5 Reviewer's summary

This study demonstrated a statistically significant difference in objectively measured LPS for both the 4mg and the 8 mg dose in comparison to placebo, which supports the idea that this drug may have an effect on sleep initiation.

I note an inexplicable increase in awakenings after sleep onset in patients when using the 4 mg dose. There is no evidence that this product has any effect on sleep maintenance.

It is of interest to note that the subjective sleep quality and subjective total sleep time results for the active treatment groups did not reflect the expected improvement despite statistically demonstrated improvement in objective LPS and objective TST.

The treatment duration was only two nights per dose. The data obtained supports the fact that this product will have an immediate effect on sleep initiation but does not provide any insight into the duration of that effect.

10.2.4 Study TL020: A Phase III, randomized, double-blind, outpatient, safety and efficacy study of TAK-375 in adults with chronic insomnia

10.2.4.1 Objective

To assess the safety and efficacy of ramelteon at doses of 8 and 16 milligrams, as compared to placebo, in patients with chronic insomnia.

10.2.4.2 Study design

A randomized, double-blind, placebo-controlled, fixed-dose, parallel group multi-center 35-nights outpatient study in patients with chronic primary insomnia

10.2.4.3 Study population and procedures

10.2.4.3.1 Study duration

Each participant was to be studied for 49 days, comprised of a 7 night single-blind placebo run-in, 35 nights of double-blind treatment followed by 7 nights of placebo run-out.

10.2.4.3.2 Entry criteria

Inclusion criteria

1. Healthy adults ≥18 and <65 years old
2. Women of child-bearing potential must agreed to use appropriate birth control (barrier methods, hormonal contraceptives and/or intrauterine devices)during the study for the remainder of the cycle after dosing. Females of childbearing potential must have had a negative serum pregnancy test at screening and within 7 days of the first dose of single-blind medication.
3. Chronic insomnia as defined by DSM IV-TR for at least 3 months and a history of daytime complaints associated with disturbed sleep
4. A subjective sleep latency (sSL) greater than or equal to >45 minutes, and a subjective total sleep time (sTST) less than 6.5 hours/night for at least 3 nights during the week of the lead-in period, based upon subject diary
5. Habitual bedtime between 8:30 PM and 12 AM
6. Body mass Index between 18 and 34, inclusive
7. Able to write, read and speak English
8. Capable of understanding and complying with the protocol
9. Signed informed consent document at screening

Exclusion criteria

1. Pregnancy or lactation
2. Known hypersensitivity to TAK-375 or related compounds including melatonin
3. Previous participation in a study involving TAK-375

4. Use of any other investigational drug within 30 days or 5 half-lives prior to the first day of single-blind study medication, whichever was longer
5. Sleep schedule changes required by employment within 3 months prior to the first day of single-blind study medication
6. Had flown across greater than 3 time zones within the past 7 days
7. Participation in a weight-loss program or alteration of exercise routine within 30 days prior to the first day of single-blind study medication
8. History of COPD, seizures, drug addiction, sleep apnea, nocturnal myoclonus, restless leg syndrome, schizophrenia, bipolar disorder, or mental retardation
9. History of psychiatric disorder (including anxiety or depression) within the previous 12 months
10. History of drug addiction or drug abuse within the past 12 months
11. History of alcohol abuse within past 12 months, as defined in the DSM-IV-TR and/or regularly consumes 4 or more alcoholic drinks/day
12. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease, unless currently controlled and stable with protocol allowed medication 30 days prior to the first day of single-blind study medication
13. Use of tobacco products during nightly awakenings
14. Use of CNS-active drugs within 3 weeks (or 5 half-lives of the drug, whichever is longer) of single blind medication. The medications in question must not have been used to treat psychiatric diseases.
15. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the three weeks prior to screening.
16. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
17. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody (only IgM was exclusionary) or HCV antibodies
18. Any additional conditions that in the investigator's opinion would affect sleep-wake function, prohibit the subject from completing the study or not be in the best interest of the subject

10.2.4.3.3 Study medications

- TAK-375 8 mg
- TAK-375 16 mg
- Placebo

Prohibited concurrent therapy

The use of the following medications was prohibited beginning 3 weeks prior to the first day single-blind study medication and during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory

stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, CNS active drugs (including herbal preparations with CNS effects), narcotic analgesics and all beta blockers, St. John's wort, kava-kava, gingko biloba, any other supplements, OTC or prescription medications that may interfere with the evaluation of the study medication.

Medications prohibited within 5 days prior to first day of single-blind study medication and during the study included melatonin or other drugs or supplements known to affect sleep/wake function.

10.2.4.3.4 Study procedures

Initial screening period (Day -21 to Day -9)
During this visit, patients who meet the eligibility criteria will be asked to provide informed consent before undergoing a full physical examination including weight and height, providing a medical history including a sleep history, as well as providing blood for clinical laboratory testing. At the screening visit, serum HCG and a hepatitis panel were to be done in addition to chemistry and hematology testing.

Vital signs were to be assessed at this and all subsequent visits.

A 12-lead electrocardiogram was to be performed at this visit.

Single-blind placebo lead-in period (Day-7 to Day -1)
A baseline symptom assessment will be done at this visit. Subjects were expected to begin recording data including bedtime, subjective sleep latency (sSL), subjective total sleep time (sTST), subjective sleep quality (sSQ), subjective number of awakenings (sNAW) and subjective ease of falling back to sleep. They were expected to continue recording this data through the end of the study.

Double-blind treatment period (Day 1 to Day 35)
Patients will be randomized to one of 3 treatment arms: 8 mg TAK-375, 16 mg TAK-375, or placebo. They will be instructed to take one tablet of study medication each night before bed. The participants were to be instructed not to take the medication with alcohol or caffeine.

All clinic visits were to be scheduled based upon the Day 1 visit, though any given visit might be completed within 2 days before or after the scheduled date.

Urine and blood for clinical laboratory testing was to be obtained at the Day 1 visit, the week 2 visit (Day 15 +/- 2 days), and the week 5 visit (Day 36 +/- 2 days).

A Tyrer benzodiazepine withdrawal symptom questionnaire (BWSQ), and a clinical global impression (CGI) were to be completed at this visit and at all subsequent visits.

An abbreviated physical examination was to be done at the Week 2 visit.

A 12-lead electrocardiogram was to be performed at the Week 5 visit.

Single-blind placebo run-out period (Day 36 to Day 42)
This period is designed to assess for possible rebound insomnia as well as any withdrawal effects after abrupt drug discontinuation.

Final visit (Day 43)
A full physical examination including weight was to be done at this visit. Urine and blood for clinical laboratory testing was to be obtained at this visit. Additionally, a 12-lead electrocardiogram was to be performed at this visit.

10.2.4.3.5 Efficacy parameters

Primary efficacy variable

- Average subjective sleep latency.

Secondary efficacy variables

- Subjective total sleep time
- Subjective sleep quality
- Subjective number of awakenings
- Subjective Ease of falling back to sleep
- Clinical global impression

10.2.4.3.6 Statistical analysis

The sponsor planned to analyze the intent-to-treat (ITT) population, which was defined as all subjects who are randomized and receive at least one dose of double-blind study medication. The efficacy analyses were to be based on a LOCF set, though analyses on observed data was also to be presented as well.

Baseline values were defined as the average of non-missing observations from eh single-blind placebo lead-in period. The protocol defined weekly time windows as nights 1-7, 8-14, 15-21, 22-28 and 29-last dose of double-blind study medication. The average of the non-missing data for a given weekly time window was to be analyzed when available. When data was unavailable for a given time window, the values from the last available time window were to be carried forward.

The drug efficacy was to be assessed using Fisher's protected least significant differences (LSD) to control the Type I error, using Week 1 as the primary time point. Maintenance of efficacy was to be assessed at weeks 3 and 5 with a sequential testing procedure. Analysis of log transferred values and non-parametric analysis.

Comparisons between the treatment groups were to be made using t-tests with least squares means and standard errors derived from an ANCOVA model: parameter=baseline + center + treatment.

Daily observations from each day of the single-blind placebo run-out period were to be used in the assessment of rebound insomnia.

10.2.4.3.7 Protocol amendments

The first amendment was dated 20 January 2003.
In this amendment, the sponsor did the following:

- Clarified the washout period for exclusionary medications
  - The washout period was changed to one week or 5 drug half-lives whichever was longer in all cases.
- Incorporated preliminary information on the importance of the CYP1A2 and CYP3A4 pathways from potential drug interaction studies
- Requested the maintenance of a temperature log for the study medication storage area
- Clarified the fact that fasting was preferable but not required prior to laboratory sample collection
- Specified that a properly trained person other than the investigator would be permitted to complete the CGI
- Clarified the SAE reporting process
- Changed the planned analysis for the BWSQ from an analysis of change from baseline to an analysis of change from the last week on double-blind study medication.
- Clarified the planned display of treatment emergent adverse events
- Corrected the number of study medication dosing nights in the informed consent document
- Clarified the compensation and treatment for injury process outlined in the sample informed consent form
- Corrected information on the double-blind study medication labels
- Corrected administrative discrepancies

The second amendment was dated 15 September 2003.
In this amendment the sponsor did the following:

- Corrected administrative discrepancies
- Re-inserted packaging information which had been mistakenly omitted from Amendment No. 1

10.2.4.3.8 Changes to the planned statistical analysis

The sponsor reported that problems with data collection were discovered during the study.

The protocol specified weekly time windows as nights 1-7, 8-14, 15-21, 22-28 and 29-last dose of double-blind study medication and that the average of the non-missing data for a given weekly time window was to be analyzed when available.

"Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. For example, all data recorded on the CRF for Week 1 were analyzed for that visit. No recorded dates were checked. The SAP that was finalized for the study, prior to unblinding, included these changes. (final study report, section 9.8)"

10.2.4.4 Study results

10.2.4.4.1 Trial characteristics

This study began on 09 January 2003 and ended on 26 September 2003. A total of 79 study sites, all of which were in the United States of America, enrolled patients.

The plan was to enroll 810 patients. The final ITT and safety population had 848 subjects. The per-protocol population (PP) had only 695 patients.

10.2.4.4.2 Demographics

Table 62: Demographics for study PNFP-020

	Placebo (PBO) N=287	**Ramelteon 8 mg N=277**	**Ramelteon 16 mg N=284**
Age (years)			
Mean (SD)	44.0 (12.38)	43.3 (12.3)	44.2 (11.99)
Sex			
Male	126 (44%)	112 (40%)	111 (39%)
Female	161 (56%)	165 (60%)	173 (61%)
Ethnicity			
White	188 (66%)	190 (69%)	203 (72%)
Black	46 (16%)	54 (20%)	44 (16%)
Hispanic	45 (16%)	21 (8%)	26 (9%)
Asian	5 (2%)	7 (3%)	6 (2%)
Native American	1 (<1%)	1 (<1%)	0
Other	2 (1%)	4 (1%)	5 (2%)

A total of 137 patients did not complete the study:

- 25 patients withdrew due to adverse events
  - 7 in the placebo group
  - 7 in the 8 milligram group
  - 12 in the 16 milligram group
- 24 due to lack of efficacy
  - 9 in the placebo group
  - 10 in the 8 milligram group
  - 5 in the 16 milligram group
- 25 due to protocol deviations
  - 5 in the placebo group
  - 13 in the 8 milligram group
  - 7 in the 16 milligram group
- 31 withdrew consent
  - 15 in the placebo group
  - 8 in the 8 milligram group
  - 9 in the 16 milligram group

- 21 were lost to follow-up
  - 5 in the placebo group
  - 6 in the 8 milligram group
  - 11 in the 16 milligram group
- 10 due to "other" reasons
  - 4 in the placebo group
  - 2 in the 8 milligram group
  - 4 in the 16 milligram group
- 1 patient, in the placebo group, was terminated from the study

There were no statistically significant differences between the groups in the level of habitual tobacco, alcohol or caffeine use. The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, quality of usual sleep and decreased ability to function associated with sleep. There were no significant differences between the treatment groups when the use of prior and /or concomitant medications was reviewed.

10.2.4.4.3 Protocol violations

Over half of the study participants had a protocol deviation reported by the study investigators, see table below. The majority of the specified deviations were patients who did not have return study visits within the specified time periods. The "other" category was comprised mostly of assessments that were not done or were done at the incorrect time.

Table 63:

	Treatment			
Deviation Category	**Placebo n=287**	**Ramelteon 8 mg n=277**	**Ramelteon 16 mg n=284**	**Total N=848**
Number of subjects with any deviations	163	156	172	491
Study medication	51	37	39	127
Visit date window	71	54	76	201
Prohibited medication	20	22	19	61
Other	96	102	104	302

Study report table 10.c

Upon review of the data (see table below), the sponsor detected additional protocol deviations, which included 49 patients who did not meet the inclusion criteria which stated that the patient had to have primary insomnia of at least 3 months duration and a history of daytime complaints associated with disturbed sleep as well as 47 patients who did not meet the inclusion criteria which stated that the subject had to have a sSL greater than or equal to 45 minutes and a sTST less than or equal to 6.5 hours/night for at least 3 nights during the week of the lead-in period.

Table 64:

Deviation Category	Treatment: Placebo n=287	Ramelteon 8 mg n=277	Ramelteon 16 mg n=284	Total N=848
Number of subjects with any deviations	66	70	73	209
Violated 1 or more inclusion/exclusion criteria	43	49	43	135
Received prohibited medications	24	22	27	73
Had a low study medication compliance (a)	9	7	9	25

Study report table 10.d

[*Reviewer's note: The protocol deviations discovered by the sponsor's review of the data may have affected the efficacy results. The protocol deviations reported by the investigators are unlikely to have done so. The sponsor did analysis of the ITT population as well as the PP population.*]

10.2.4.4.4 Efficacy endpoints

All 848 patients were included in the ITT population: 153 patients were excluded from the PP population.

Primary endpoint

The primary endpoint was the Subjective sleep latency (sSL), as recorded in subject diaries, from week 1 of double blind treatment. No statistically significant treatment effect for active drug was seen (p=0.602 overall, with a p-value of 0.888 for the 8 mg group and 0.349 for the 16 mg group).

The sponsor evaluated the trial using observed data as opposed to imputing data using LOCF. There were no statistically significant differences apparent with that analysis. The sponsor performed confirmatory log-transformation and non-parametric analysis. The results of said analyses confirmed the original finding.

The sponsor performed a categorical analysis of the data after separating the patients in to those who had sSL of $\leq$30 minutes versus those who had sSL > 30 minutes. There were no statistically significant differences apparent with that analysis.

Secondary Endpoints

- Subjective sleep latency, per subject diary over the week preceding the DAY 15, Day 22, Day 29 and Day 36 visits.

No statistically significant treatment effect for active drug was seen at any of the time points assessed. Additionally, the sponsor reports that no distinct trends or meaningful shifts in sSL were observed.

- Subjective number of awakenings (sNAW)

Statistically significant decreases in subjective sleep latency for both the 8 mg and the 16 mg dose as compared to placebo were seen at week one using the LOCF analysis. These decreases did not persist through the other timepoints.

- Subjective total sleep time (sTST)

No statistically significant treatment effect for active drug was seen at any of the time points assessed.

- Subjective ease of falling back to sleep after awakening

A statistically significant treatment effect for active drug was seen at Week 3 for the 8 mg dose only. The sponsor felt that the "difference was small not meaningful (study report p.87/1336)", noting that no significant differences were noted at any of the other time-points assessed.

- Subjective sleep quality (sSQ)

No overall statistically significant treatment effect was seen when active drug at any dose was compared to placebo.

Clinical global impression
This included global rating of change of condition, of severity of illness, of therapeutic effect and of side effects. No overall statistically significant treatment effect was seen when active drug at any dose was compared to placebo.

[*Reviewer's comment: The results presented above reflect analysis of the ITT population. The sponsor also did analyses of the smaller PP population. The latter analyses did not produce any significant changes in the findings.*]

10.2.4.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.4.5 Reviewer's Summary

This outpatient study in adults failed to meet its' primary efficacy endpoint as evaluation of subjective sleep latency showed no demonstrable difference from placebo whether patients received 8 or 16 milligrams of ramelteon.

10.2.5 Study TL021: A phase III, randomized, double-blind placebo-controlled, PSG plus outpatient study to determine the safety and efficacy of TAK-375 in adults with chronic insomnia

10.2.5.1 Objectives

To assess the safety and efficacy of ramelteon at doses of 8 and 16 milligrams, as compared to placebo, in patients with chronic insomnia.

10.2.5.2 Study design

A randomized, double-blind, placebo-controlled, fixed-dose, parallel group multi-center 35-nights PSG plus outpatient efficacy and safety study in patients with chronic insomnia

10.2.5.3 Study population and procedures

10.2.5.3.1 Study duration

Each participant was to be studied for 44 days, comprised of a 7 night single-blind placebo run-in, 35 nights of double-blind treatment followed by 2 nights of placebo run-out.

10.2.5.3.2 Entry criteria

Inclusion criteria

1. Healthy adults ≥18 and <64 years old, inclusive
2. Women of child-bearing potential must agreed to use appropriate birth control (barrier methods, hormonal contraceptives and/or intrauterine devices) during the entire study duration. Females who are not of childbearing potential must be postmenopausal for 1 year or have history of hysterectomy and/or oophorectomy.
3. Chronic insomnia as defined by DSM IV-TR for at least 3 months and a history of daytime complaints associated with disturbed sleep
4. A mean [sleep] latency of > 20 minutes on two consecutive screening nights with neither night less than 15 minutes. Also a mean of 60 minutes of wake time during the 480 minutes in bed across two nights with no night less than 45 minutes
5. A subjective sleep latency (sSL) greater than or equal to >30 minutes, and a subjective total sleep time (sTST) less than 6.5 hours/night
6. Habitual bedtime between 8:30 PM and 12 AM
7. Body Mass Index between 18 and 34, inclusive
8. Able to write, read and speak English
9. Capable of understanding and complying with the protocol
10. Signed informed consent document at screening

Exclusion criteria

1. Pregnancy or lactation

2. Known hypersensitivity to TAK-375 or related compounds including melatonin
3. Previous participation in a study involving TAK-375
4. Use of any other investigational drug within 30 days or 5 half-lives prior to the first day of single-blind study medication, whichever was longer
5. Sleep schedule changes required by employment within 3 months prior to the first day of single-blind study medication
6. Had flown across greater than 3 time zones within the 7 days prior to screening
7. Participation in a weight-loss program or alteration of exercise routine within 30 days prior to the first day of single-blind study medication
8. History of COPD, seizures, sleep apnea, schizophrenia, bipolar disorder, cognitive disorder or mental retardation
9. History of psychiatric disorder (including anxiety or depression) within the previous 12 months
10. History of drug addiction or drug abuse within the past 12 months
11. History of alcohol abuse within past 12 months, as defined in the DSM-IV-TR and/or regularly consumes 4 or more alcoholic drinks/day
12. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease, unless currently controlled and stable with protocol allowed medication 30 days prior to the first day of single-blind study medication
13. Use of tobacco products during nightly awakenings
14. Use of melatonin, or other drugs/supplements known to affect sleep/wake function within 5 days prior to the first night of single-blind study medication
15. Use of CNS-active drugs within 3 weeks (or 5 half-lives of the drug, whichever is longer) of single blind medication. The medications in question must not have been used to treat psychiatric diseases.
16. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the three weeks prior to screening.
17. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
18. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody (only IgM was exclusionary) or HCV antibodies
19. A positive urine drug screen including alcohol at screening or a positive breathalyzer test at each check-in
20. An apnea-hypopnea index (per hour of sleep) > 10 as seen on PSG, on the first night of PSG screening
21. Periodic leg movement (PLM) with arousal index (per hour of sleep) > 10 as seen on PS, on the first night of PSG screening
22. Any additional conditions that in the investigator's opinion would affect sleep-wake function, prohibit the subject from completing the study or not be in the best interest of the subject

10.2.5.3.3 Study medications

- TAK-375 8 mg
- TAK-375 16 mg
- Placebo

Prohibited concurrent therapy
The use of the following medications was prohibited beginning 3 weeks prior to the first day single-blind study medication and during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, CNS active drugs (including herbal preparations with CNS effects), narcotic analgesics and all beta blockers, St. John's wort, kava-kava, gingko biloba, any other supplements, OTC or prescription medications that may interfere with the evaluation of the study medication.

Medications prohibited within 5 days prior to first day of single-blind study medication and during the study included melatonin or other drugs or supplements known to affect sleep/wake function.

10.2.5.3.4 Study procedures

Initial screening period including PSG (Day -21 to Day -7)
The initial screening was to consist of a physical examination, laboratory testing and a 12-lead ECG.

Single-blind placebo lead-in period (Day-7 to Day -1)
Patients who meet the screening inclusion criteria were to receive single-blind placebo medication and to undergo PSG screening on nights -7 and -6.

Any subject who failed PSG criteria on night -7 was to be removed from the study as a screening failure. Those subjects who met criteria on both nights -7 and -6 were to be given additional single-blind placebo medication to be taken on nights -5 to -1.

Patients who met the clinical and PSG screening criteria were to be randomized into one of the three treatment arms: ramelteon 8 mg, ramelteon 16 mg or placebo.

Patients were to be asked to complete the VAS, DSST, memory recall tests and sleep questionnaire at the screening PSG and at each clinic visit.

The Tyrer Benzodiazepine withdrawal symptom questionnaire (BWSQ) was to be completed at the PSG screening visit and at all subsequent PSG visits.

Double-blind PSG treatment period (Day 1 to Day 35)
This study was to incorporate 4 PSG treatment periods. PSG recordings were to be done on Nights 1, 2, 15, 16, 29 and 30. Patients were to arrive at the sleep laboratory 2 to 2.5 hours before their usual bedtime. While at the sleep laboratory, prior to dosing in the evening, subjects were to

complete the VAS, DSST and memory recall test. Upon completion of the testing instruments, a single oral dose of study medication was to be administered 30 minutes prior to the usual bedtime. A PSG recording was then to be run uninterrupted for 8 hours. If necessary, the patient was to be awakened after the 8 hours of PSG recording. Upon awakening, subjects were to complete the VAS, DSST, memory recall test and a post-sleep questionnaire. They were them to be discharged with instructions to return for the second night of recording that evening. The second night of recording would be a duplicate of the first.

Between the scheduled PSG recordings, the patients were to take the study medication nightly at home. Throughout the course of the study, subjects were to be asked to maintain subject diaries and return for periodic clinic visits at which the diary entries, the concomitant medication history and any adverse events would be reviewed.

The diaries were to be used to collect information on study medication compliance, bedtime, time to sleep onset, sleep quality, number of awakenings and ease of falling back to sleep.

Final visit (Day 38)
Once the patients had completed 35 days of double blind treatment, they were to report to the sleep laboratory for PSG recordings and single-blind placebo medication on Days 36 and 37. This single-blind run-out period was to be used to evaluate for rebound insomnia and or withdrawal effects. The final evaluations were to take place on Day 38.

10.2.5.3.5 Efficacy parameters

Primary efficacy variable
Latency to persistent sleep

Secondary efficacy variables
PSG
Total sleep time
Sleep efficiency
Awake time after persistent sleep
Number of awakenings after persistent sleep
Subjective (from post-sleep questionnaire)
Sleep latency
Total sleep time
Sleep quality
Awake time
Number of awakenings
Ease of falling back to sleep

10.2.5.3.6 Statistical analysis

The intent-to-treat (ITT) population was the population to be used for analysis of efficacy and safety. While the ITT population was to consist of all randomized subjects who received at least one dose of double-blind study medication, in practice the analyses for a given variable would only include those patients who had a measurement for that variable.

The efficacy analysis, analysis of sleep architecture variables and the special safety variables from the post-sleep questionnaire were to be based on LOCF data, though the observed data would also be presented. ANOVA with treatment and pooled center as factors was to be used to evaluate baseline characteristics of the variables.

Comparisons between treatment groups was to be made using t-tests with least square means and standard errors obtained from the following ANCOVA model:
parameter=baseline+center+treatment

The mixed model procedure (PROC MIXED) with center and treatment effects fixed was to be applied. Type III sums of squares was to be used to generate the ANCOVA results. Since the primary efficacy analysis time point was week 1, the average of the available observations for Week 1 was to be analyzed. Maintenance of efficacy was to be assessed at week 3 and 5 using a sequential testing procedure.

Safety analyses were to be based upon observed data.

Weekly time windows, i.e. nights 1-7, 8-14, 15-21, 22-28, 29-last dose of double-blind study medication, were defined for the collection of subjective assessment variables. Any data collected in conjunction with the PSG assessments was to be analyzed according to the scheduled visit rather than the time window.

The average of the available observations from the single-blind lead in period was to be considered the baseline. Observations from each day of the single-blind placebo run-out period were to be used to assess rebound.

No interim analysis was planned.

10.2.5.3.7 Protocol amendments

The protocol amendment, dated 18 February 2003, made the following changes:

- Added updated references
- Added additional central PSG readers
  - The original protocol listed [redacted] of Sleep Disorders and Research Center as the Central PSG reader.
  - The amendment changed Dr. [redacted] facility to the coordinating center and added three other individuals as central scorers: Drs. [redacted] Zammit.
- Clarified the single-blind dosing period
- Clarified subjective variables would be collected from the post-sleep questionnaire as well as the sleep diary
- Allowed those subjects with a $\geq$ 20 minute mean latency [to persistent sleep]
- Clarified the washout period for exclusionary medications was within one week or 5 half-lives whichever was longer
- Incorporated preliminary information from potential drug interaction studies
- Corrected the urine drug screen

- Requested the maintenance of a temperature log for the study medication storage area
- Clarified fasting requirements prior to laboratory sample collection
- Clarified the SAE reporting process
- Clarified the planned analysis for the BWSQ, with withdrawal to be calculated as change from the mean if Day 29 and Day 30 to Day 36 and Day 37 separately in the total score
- Clarified the planned display of adverse events
- Clarified final termination procedures
- Added a serum pregnancy test to the final visit procedures
- Clarified the data to be collected on the case report form to state that the VAS and DSST were to be practiced twice nightly during screening but only the second practice of each screening night would be captured on the CRF.
- Clarified definitions of PSG parameters
- Added a definition for awake time after persistent sleep i.e. the number of wake minutes after the onset of persistent sleep prior to the end of the recording
- Corrected minor administrative discrepancies e.g. titles, spelling errors

[Reviewer's note: Drs. [ ] Zammit [ ] are listed as central scorers. Dr. Zammit (site # 10912) enrolled 25/405 patients in this protocol. Dr. [ ] (site # [ ]) enrolled [ ] patients in this protocol. Dr. [ ] (site # [ ]) enrolled [ ] patients in this protocol. A request for information was sent to Takeda (on May 11, 2005) to determine who was responsible for reviewing the PSG recording for the patients enrolled at the sites run by the central scorers. Takeda responded that Dr. [ ] was responsible for reviewing the recordings from Drs. Zammit [ ] sites. Dr. Zammit reviewed the recordings from Dr. [ ] site.]

The administrative change, dated 01 August 2003, corrected a line in the section on storage of clinical supplies which erroneously referred to 4 mg tablets. This was corrected to read 8 mg tablets, the dose used in this study.

10.2.5.3.8 Changes to the planned statistical analysis

The sponsor reported that the statistical analysis plan was modified to account for problems with data collection which were discovered during the study.

The protocol specified weekly time windows as nights 1-7, 8-14, 15-21, 22-28 and 29-last dose of double-blind study medication and that the average of the non-missing data for a given weekly time window was to be analyzed.

"Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. No recorded dates were checked. "With diaries being returned to the clinic on Days 15, 29, and 36, the appropriate labels for the diary data during treatment are "Weeks 1-2," "Weeks3 -4" and "Week 5." The SAP that was finalized for the study, prior to unblinding, included these changes. (final study report, section 9.8)"

After the results from this study were reviewed, the sponsor performed supplemental analyses to distinguish the findings for subjective data in the clinic (post-sleep questionnaire) and subjective data at home (sleep diaries). These *post hoc* analyses were not part of the SAP for the study.

10.2.5.4 Study results

10.2.5.4.1 Trial characteristics

This study began on 20 January 2003 and ended on 24 September 2003. A total of 29 study sites, all of which were in the United States of America, enrolled patients.

The plan was to enroll 390 patients. The final ITT and safety population had 405 subjects. The per-protocol population (PP) had only 156 patients.

10.2.5.4.2 Demographics

Table 65: Demographics for study PNFP-021

	Placebo (PBO) N=131	**Ramelteon 8 mg N=139**	**Ramelteon 16 mg N=135**
Age (years)			
Mean (SD)	39.7 (11.96)	38.0 (11.53)	40.2 (12.44)
Sex			
Male	30 (23%)	57 (41%)	46 (34%)
Female	101 (77%)	82 (59%)	89 (66%)
Ethnicity			
White	79 (60%)	87 (63%)	82 (61%)
Black	21 (16%)	19 (14%)	23 (17%)
Hispanic	27 (21%)	27 (19%)	27 (20%)
Asian	3 (2%)	3 (2%)	2 (2%)
Native American	0	1 (<1%)	0
Other	1 (<1%)	2 (1%)	1(<1%)

(modification of table 10b from the final study report)

A total of 38 patients did not complete the study:

- 7 patients withdrew due to adverse events
  - 2 in the placebo group
  - 4 in the 8 milligram group
  - 1 in the 16 milligram group
- 2 due to lack of efficacy , both in the placebo group
- 7 due to protocol deviations
  - 1 in the placebo group
  - 4 in the 8 milligram group
  - 2 in the 16 milligram group
- 18 withdrew consent

- 6 in the placebo group
- 9 in the 8 milligram group
- 4 in the 16 milligram group

- 1 was lost to follow-up from the placebo group
- 2 due to "other" reasons
  - 1 in the placebo group was withdrawn due to noncompliance
  - 1 in the 8 milligram group took a job that required travel during visit 5

There were statistically significant differences at baseline among the treatment groups for the following demographic characteristics only: height (p=0.005); weight (p=0.006); gender (p=0.007). There were no statistically significant differences between the groups in the level of habitual alcohol or caffeine use. A higher proportion of nonsmokers and a lower proportion of current smokers was found in the placebo group as compared to the ramelteon groups, the difference was statistically significant with a p-value=0.028. The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant sleep parameter. There were no significant differences between the treatment groups when the use of prior and /or concomitant medications was reviewed.

10.2.5.4.3 Protocol violations

The majority of the study participants had a protocol deviation reported by the study investigators, see table below. Most of the specified deviations were patients who did not have return study visits within the specified time periods. The "other" category comprised assessments that were not done or were done at the incorrect time, time to sleep after midnight, subjects who did not fast when they were supposed to, etc.

Table 66:

	Treatment			
Deviation Category	**Placebo n=131**	**Ramelteon 8 mg n=139**	**Ramelteon 16 mg n=135**	**Total N=405**
Number of subjects with any deviations	100	107	111	318
Study medication	31	42	40	113
Visit date window	20	25	23	68
Prohibited medication	10	7	9	26
Other	88	87	99	274

Study report table 10.c

Upon review of the data (see table below), the sponsor detected additional protocol deviations, which included 225 patients who did not meet the inclusion criteria which stated that the subject had to have latency ≥20 minutes on the two PSG screening nights with neither night <15 minutes and a mean of 60 minutes of wake time with no less than 45 minutes a night.

Table 67:

Deviation Category	Treatment: Placebo n=131	Ramelteon 8 mg n=139	Ramelteon 16 mg n=135	Total N=405
Number of subjects with any deviations	78	98	84	260
Violated 1 or more inclusion/exclusion criteria	71	90	77	238
Received prohibited medications	15	17	16	48
Study medication compliance <70%	4	3	6	13
Received wrong treatment or dose	0	0	1	1

Study report table 10.d

[*Reviewer's note: The protocol deviations discovered by the sponsor's review of the data may have affected the efficacy results. The protocol deviations reported by the investigators are unlikely to have done so. The sponsor did analysis of the ITT population as well as the PP population.*]

Three pregnancies were reported during this study:
Subject 12700/019 had not received any study medication prior to the detection of her pregnancy. No additional information is available on the course of her pregnancy or its outcome.

Subject 09894/037 had received placebo from 20 June 2003 to 26 June 2003. Her pregnancy was confirmed prior to randomization. No additional information is available on the course of her pregnancy or its outcome.

Subject 12721/211327 had been randomized to ramelteon 8 mg. She ingested study drug from 9 June 2003 to 22 July 2003. Her pregnancy was confirmed on [redacted], and she was withdrawn from the study that day. The pregnancy was terminated on [redacted]

10.2.5.4.4 Efficacy endpoints

The sponsor reports having included baseline values as a covariate in the ANCOVA model of the analysis of the primary and secondary variables. All analyses were based upon LOCF data. The sponsor also did confirmatory analyses of the observed data, the results form those confirmatory analyses were consistent with the LOCF analysis as per the sponsor.

Prior to unblinding the data, centers with fewer than 9 subjects at week 1 were pooled with geographically adjacent centers. Out of 29 participating centers, 17 centers were pooled to form 7-pooled centers. Treatment-by –center interaction was evaluated in the analysis of latency to persistent sleep at week 1.

Primary endpoint: Latency to persistent sleep (LPS)
A statistically significant overall treatment effect in favor of active drug, in the ITT population based upon LOCF data, was seen when active drug was compared to placebo at weeks 1 ($p<0.001$), 3 ($p<0.001$) and 5 ($p<0.003$). At weeks 1, 3, and 5 both studied doses were also superior to placebo when reviewed individually: 4 mg was statistically

significant at levels of <0.001, 0.001 and 0.007 respectively; 8 mg was statistically significant at levels of <0.001, <0.001 and 0.002 respectively.

The analysis of the observed data was consistent with the results obtained from analysis of the LOCF data. The sponsor also performed log transformation and nonparametric analyses to confirm the findings from the primary analysis. These confirmatory measures were also in agreement with the findings from the primary analysis.

When the PP population was evaluated, using LOCF data, only the ramelteon 16 mg group showed a statistically shorter LPS at weeks 1 and 3. The sponsor attributes this to the smaller sample size in the PP population.

Table 68: LPS (minutes)-ITT population

	Placebo (PBO) (n=131)	**Ramelteon 8 mg (n=139)**	**Ramelteon 16 mg (n=135)**
Baseline			
N	131	139	135
LS mean (SE)	65.3 (3.54)	64.3 (3.46)	68.4 (3.54)
Week 1			
N	131	138	135
LS mean (SE)	47.9 (2.72)	32.2 (2.67)	28.9 (2.71)
LSM-PBO (SE)		-15.7 (3.70)	-18.9 (3.73)
95% CI for difference		-22.9, -8.4	-26.3, -11.6
Week 3			
N	131	138	135
LS mean (SE)	45.5 (2.93)	32.6 (2.87)	27.9 (2.92)
LSM-PBO (SE)		-12.9 (3.98)	-17.6 (4.02)
95% CI for difference		-20.7, -5.1	-25.5, -9.7
Week 5			
N	118	124	135
LS mean (SE)	43.6 (3.39)	31.5 (2.91)	29.5 (2.96)
LSM-PBO (SE)		-11.0 (4.03)	-12.9 (4.07)
95% CI for difference		-18.9, -3.1	-20.9, -4.9

(study report table 11a)

Secondary Endpoints

- Wake time after sleep onset (WASO)

No statistically significant treatment effect was seen when TAK-375 8mg or TAK-375 16 mg was compared to placebo.

- Sleep Efficiency (SE)

Using LOCF data, a statistically significant treatment effect in favor of active drug was seen when ramelteon 8 mg (p<0.001) and ramelteon 16 mg (p<0.001) were compared to placebo in week 1.

The overall treatment effect was not seen in week 3 (p=0.145) or in week 5 (p=0.362), though the results for ramelteon at the 16 mg dose (only) did achieve significance at week 3 (p=0.0497).

- Total Sleep Time (TST)

A statistically significant treatment effect in favor of active drug was seen when ramelteon 8 mg (p<0.001) and ramelteon 16 mg (p<0.001) were compared to placebo in week 1.

The overall treatment effect was not seen in week 3 (p=0.136) or in week 5 (p=0.394), though the results for ramelteon at the 16 mg dose (only) did achieve significance at week 3 (p<0.047).

When the PP population was evaluated, using LOCF data, there were no statistically significant treatment differences seen at any of the double-blind periods.

Table 69: TST (minutes)-ITT population

	Placebo (PBO) (n=131)	**Ramelteon 8 mg (n=139)**	**Ramelteon 16 mg (n=135)**
Baseline			
N	131	139	135
LS mean (SE)	65.3 (3.54)	64.3 (3.46)	68.4 (3.54)
Week 1			
N	131	138	135
LS mean (SE)	47.9 (2.72)	32.2 (2.67)	28.9 (2.71)
LSM-PBO (SE)		-15.7 (3.70)	-18.9 (3.73)
95% CI for difference		-22.9, -8.4	-26.3, -11.6
Week 3			
N	131	138	135
LS mean (SE)	45.5 (2.93)	32.6 (2.87)	27.9 (2.92)
LSM-PBO (SE)		-12.9 (3.98)	-17.6 (4.02)
95% CI for difference		-20.7, -5.1	-25.5, -9.7
Week 5			
N	118	124	135
LS mean (SE)	43.6 (3.39)	31.5 (2.91)	29.5 (2.96)
LSM-PBO (SE)		-11.0 (4.03)	-12.9 (4.07)
95% CI for difference		-18.9, -3.1	-20.9, -4.9

(study report table 11b)

- Number of awakenings after sleep onset

No statistically significant treatment effect was seen when ramelteon 8mg or ramelteon 16 mg was compared to placebo.

- Subjective sleep latency (sSL)

The ramelteon 16 mg group was showed a statistically significant decrease in subjective sleep latency (p=0.01) during week 3. The findings from the ramelteon 8 mg group never reached statistical significance in comparison to placebo.

The sponsor performed a *posthoc* analysis of this parameter. The original analysis combined information from the sleep diaries, which were done on an outpatient basis, and the postsleep questionnaires, which were done after a night in the sleep laboratory. The *posthoc* analysis used only the information from the postsleep questionnaires.

In the *posthoc* analysis, sSL was significantly shorter in the ramelteon 8 mg group at week 1 (P<0.001), week 3(P<0.001) and week 5(P<0.001). In the posthoc analysis, sSL was significantly shorter in the ramelteon 16 mg group at week 1(P=0.009), and week 3(P=0.034).

- Subjective total sleep time (sTST)

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo.

The sponsor performed a *posthoc* analysis of this parameter. The original analysis combined information from the sleep diaries, which were done on an outpatient basis, and the postsleep questionnaires, which were done after a night in the sleep laboratory. The *posthoc* analysis used only the information from the postsleep questionnaires.

In the posthoc analysis, sTST was significantly shorter in the ramelteon 8 mg group at week 1 (P<0.001), week 3(P=0.006) and week 5 (P=0.018). In the posthoc analysis, sTST was significantly shorter in the ramelteon 16 mg group at week 1(P=0.003) only.

- Subjective sleep quality (sSQ)

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo. When the PP population was evaluated, using LOCF data, statistically significant treatment differences were seen for the ramelteon 16 mg group at week 1 (p=0497) and for the ramelteon 8 mg group at week 5 (p=0.017).

- Subjective wake time after sleep onset (sWASO)

A statistically significant treatment effect in favor of active drug was seen when ramelteon 8 mg (p=0.026) and ramelteon 16 mg (p=0.004) were compared to placebo in week 1. The overall treatment effect was not seen in week 3 or in week 5, when only the placebo group reported continued decrease in WASO.

- Subjective ease of falling back to sleep

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo.

- subjective Number of Awakenings (sNAW)

No overall statistically significant treatment effect was seen when active drug at either dose was compared to placebo.

10.2.5.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.5.5 Reviewer's Summary

This study demonstrated a statistically significant difference in objectively measured LPS for both the 8 mg and the 16mg dose in comparison to placebo, which supports the idea that this drug may have an effect on sleep initiation. There is no evidence that this product has any effect on sleep maintenance.

It is of interest to note that the subjective results for the active treatment groups did not reflect the expected improvement despite the statistically demonstrated improvement in objective findings. The apparent benefit in LPS was inconsistently seen in the 16 mg group when the PP population was evaluated.

10.2.6 TL022: A Phase III, open-label, fixed-dose study to determine the safety of long-term administration of TAK-375 in subjects with chronic insomnia

10.2.6.1 Objective

To assess the long-term safety of regular ramelteon use

10.2.6.2 Study design

An open-label, fixed-dose, multi-center, 1-year outpatient study in adult subjects with chronic insomnia

10.2.6.3 Study population and procedures

10.2.6.3.1 Study duration

12 months/patient

10.2.6.3.2 Entry criteria

Inclusion criteria

1. Healthy adults ≥18 and <65 years old
2. Capable of understanding and complying with the protocol
3. Signed informed consent document prior to performance of study procedures
4. Women of child-bearing potential must use appropriate birth control for the entire duration of the study.
5. Females who are not of childbearing potential must be postmenopausal for one year of have history of hysterectomy and/or oophorectomy.
6. Subject must, in the opinion of the investigator, require long-term treatment for insomnia
7. Chronic insomnia as defined by DSM IV for at least 3 months and daytime complaints associated with disturbed sleep
8. sSL ≥45 minutes, sTST less than 6.5 hours/night
9. Habitual bedtime between 8:30 PM and 12 AM
10. Body mass index between 18 and 34, inclusive

Exclusion criteria

1. Pregnancy or lactation
2. Known hypersensitivity to TAK-375 or related compounds including melatonin
3. Use of any other investigational drug within 30 days or 5 half-lives, (whichever was longer), although previous use of TAK-375 was permitted.
4. Sleep schedule changes required by employment within 3 months preceding Day 1
5. Had flown across greater than 3 time zones within the past 7 days

6. Participation in a weight-loss program or alteration of exercise routine within 30 days preceding Day 1
7. History of seizures, sleep apnea, COPD, restless leg syndrome, schizophrenia, bipolar disorder, mental retardation, or cognitive disorder
8. History of psychiatric disorder (including anxiety or depression) within the previous 12 months
9. History of alcohol abuse within past 12 months and/or regularly consumes 4 or more alcoholic drinks/day
10. History of drug addiction or drug abuse within the past 12 months
11. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic diseaseunless currently controlled and stable with protocol-allowed medication 30 days prior to Day 1 of study medication
12. Use of tobacco products during nightly awakenings
13. Use of melatonin or other drugs or supplements known to affect sleep/wake function within 5 days (or 5 half-lives, which ever is longer) prior to Day 1
14. Subjects taking central nervous system medication must have completed a pre-study washout period of 3 weeks (or 5 half-lives of the drug, whichever is longer) prior to Day 1. The medications in question must not have been used to treat psychiatric diseases.
15. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the three weeks prior to screening.
16. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
17. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody or HCV antibodies
18. Any additional conditions that in the investigator's opinion would either prohibit the subject from completing the study or not be in the best interest of the subject

10.2.6.3.3 Study medications

- Ramelteon 8 mg
- Ramelteon 16 mg

Prohibited concurrent therapy

The use of the following medications was prohibited beginning 3 weeks prior to Day 1 and during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, herbal preparations with CNS effects, narcotic analgesics and all beta blockers, St. John's wort, kava-kava, gingko biloba, OTC or prescription medication that may interfere with the evaluation of the study medication.

The use of melatonin or other drugs/supplements known to affect sleep/wake function was prohibited for the period within 5 days prior to Day 1 through the end of study participation.

10.2.6.3.4 Study procedures

The sponsor planned to enroll 1000 patients with chronic insomnia for participation in this study.

Previous participants in studies TL-005, TL-017, TL020, TL-021 and TL-025 were permitted to participate in this study as well if they had completed all final visit procedures for the previous study within 21 days of the treatment initiation visit for this study. These subjects, referred to as open label extension subjects, were to begin this study at the baseline lead-in visit and did not need to repeat all screening procedures.

At the screening visit, physical examinations, laboratory tests and an electrocardiogram were to be done. Within 14 days of screening, patients were to begin recordings in a sleep diary for one week.

If eligibility were to be maintained, the subjects were to be given study medication (8 mg for patients over 65 years and 16 mg for patients between 18 and 64 years) as well as additional sleep diaries.

Patients were instructed to take one dose of study medication regularly for 12 months. The sponsor defined regular nightly dosing as administration of study medication 3 to 7 night/week. Over the 12 month period, subjects were to return to the clinic for monthly assessment. At the end of the 12-month period, study medication was to be discontinued and patients were to complete a 2-night single blind placebo run-out period to assess for possible rebound insomnia.

10.2.6.3.5 Study endpoints

Primary

Adverse events, changes in vital signs, laboratory test, electrocardiograms and physical exam findings during treatment

Secondary

Subjective sleep assessments per subject diaries over the week preceding each visit
Clinical global impression

10.2.6.3.6 Statistical analysis

An intent-to-treat population, consisting of all subjects who received at least one dose of study medication, was to be analyzed for safety and efficacy.

The safety analysis was to be based upon observed data.

The LOCF data set was to be analyzed for efficacy variables.

Interim analyses are planned for the study.

10.2.6.3.7 Protocol amendments

The protocol amendment, dated 19 August 2002, made the following substantive changes in addition to minor administrative changes:

- To include preliminary results of 24-month rodent carcinogenicity studies
- To improve consistency in the collection of diary data for the Phase III protocols
- To inform potential study subjects of preliminary results of long-term rodent studies
- Minor administrative changes

The protocol amendment, dated 14 April 2003, made the following substantive changes in addition to minor administrative changes:

- To add abbreviations to the list of abbreviations and terms
- To clarify the use of endocrine measurements
- To incorporate additional information on the potential endocrine effects of TAK-375
- To allow subjects completing protocol TL-032 to enter this protocol
- To incorporate preliminary information from potential drug interaction studies
- To add additional laboratory procedures to evaluate whether TAK-375 affects endocrine function
- To decrease the frequency for CGI collection
- To incorporate the use of a menstrual diary for all premenopausal females
- To explain in the sample informed consent that placebo will be given at some point during the study
- To incorporate the definition of an adrenal adverse event and the reporting instructions for adrenal adverse events
- To clarify the definition of exposure to study drug
- To inform study subjects of the endocrine tests in the TAK-375 multiple-dose pharmacokinetic study

10.2.6.4 Study results

This study was ongoing at the time of the 120-day safety update, therefore no final study results are available. Preliminary findings have been incorporated into the review where appropriate.

10.2.7 Study TL023: A Phase III, randomized, double-blind, placebo-controlled, multi-center single-dose study of TAK-375 in healthy adult volunteers in a sleep lab model of transient insomnia

10.2.7.1 Objectives

To evaluate the safety and efficacy of ramelteon after single dose night-time administration of ramelteon (8 mg or 16 mg) compared with placebo in normal healthy adults naïve to a sleep laboratory environment

10.2.7.2 Study design

A randomized, double-blind, placebo-controlled, single-dose, parallel-group, multi-center study.

10.2.7.3 Study population and procedures

10.2.7.3.1 Study duration

2 days per patient

10.2.7.3.2 Entry criteria

Inclusion criteria

1. Healthy adults between 18 and 64 years old, inclusive
2. Females of childbearing potential must use appropriate birth control during the study. Females who are not of childbearing potential must be postmenopausal for 1 year or have a history of hysterectomy and/or oophorectomy.
3. Usual total sleep time between 6.5 and 8.0 hours, inclusive
4. Usual sleep latency of less than 30 minutes
5. Habitual bedtime between 8:30 PM and 12 AM
6. Body Mass Index between 18 and 34, inclusive
7. Capable of understanding and complying with the protocol
8. Signed informed consent document at screening

Exclusion criteria

1. History of insomnia
2. Pregnancy or lactation
3. Previous sleep laboratory experience
4. Known hypersensitivity to TAK-375 or related compounds including melatonin
5. Previous participation in a study involving TAK-375
6. Participation in an investigational study and/or taken any investigational drug within 30 days or five half-lives, whichever is longer, prior to Day 1
7. Epworth sleepiness scale of >10

8. Sleep schedule changes required by employment within 3 months preceding Day 1 check-in
9. Flown across >3 time zones within the past 7 days
10. Participation in a weight-loss program
11. Alteration of exercise program within 30 days preceding Day 1 check-in
12. History of seizures, sleep apnea, COPD, restless leg syndrome, schizophrenia, bipolar disorder, mental retardation or cognitive disorder.
13. History of a psychiatric disorder (including anxiety or depression) that may be associated with sleep disturbance
14. History of drug addiction or drug abuse within the past 12 months
15. Physical or psychiatric disorder that may be associated with a sleep disturbance
16. Evidence of a significant illness including neurological, hepatic, renal , endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease
17. Use of tobacco products during nightly awakenings
18. Use of melatonin, or other drugs or supplements known to affect sleep/wake function or consumption of grapefruit/grapefruit juice within 5 days prior to day 1
19. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. Subjects were expected to report all prescription and OTC medications taken in the 3 weeks prior to screening.
20. Clinically important abnormal findings in physical examination, ECG variables or clinical laboratory tests.
21. A positive test for hepatitis panel including HAV antibody (only positive IgM was exclusionary), HBV surface antibody (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody or HCV antibodies
22. A positive urine drug screen including alcohol at screening or a positive breathalyzer test at check-in
23. Any other conditions that in the investigator's opinion would affect sleep-wake function, prohibit the subject from completing the study or make study participation not in the best interests of the subject.

10.2.7.3.3 Study medications

Prohibited concurrent therapy

The use of the following medications was prohibited beginning 3 weeks prior to Day 1 and during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, herbal preparations with CNS effects, narcotic analgesics and all beta blockers, St. John's wort, kava-kava, gingko biloba, OTC or prescription medication that may interfere with the evaluation of the study medication.

The use of melatonin or other drugs/supplements known to affect sleep/wake function was prohibited for the period within 5 days prior to Day 1 through the end of study participation.

The consumption of grapefruit/grapefruit juice was prohibited for the period within 5 days prior to Day 1 through the end of study participation.

Use of alcohol/caffeine was prohibited for the 10 hours preceding administration of study drug.

10.2.7.3.4 Study procedures

Subjects were to come for a screening visit between 5 and 21 days prior to Study Day 1. At that visit, they were to provide a complete medical history. An examination including assessment of body weight and vital signs was to be done along with clinical laboratory evaluation. Urine was to be obtained for pregnancy screening and drug screening. A 12-lead ECG was to be performed. Two practice DSST were to be performed.

Eligible subjects checked into a sleep laboratory on Day 1 approximately 90 to 120 minutes before their usual bedtime. Urine was to be obtained for drug screening. Subjects were to have ingested a moderate meal prior to entering the sleep laboratory. They were expected to fast from the time of dosing until the completion of the procedures on study day 2.

Study participants were to receive the assigned study medications 30 minutes prior to their usual bedtime. The lights were to be turned out at the individual subject's usual bedtime and PSG recording was to be performed over the subsequent 8 hours.

Approximately 45-60 minutes after awakening on Day 2, subjects were to complete the VAS, DSST and post-sleep questionnaire. Subsequent to that, an ECG, blood draws, and a physical examination were to be completed. Patients were then to be discharged.

10.2.7.3.5 Efficacy parameters

The primary efficacy parameter was latency to persistent sleep.

The secondary efficacy parameters were total sleep time, sleep efficiency, awake time after sleep onset of persistent sleep, and number of awakenings after persistent sleep and percentage of sleep in each sleep stage as determined by PSG recording. Subjective assessments such as time to sleep onset, total sleep time restorative nature of sleep, awake time, number of awakenings subjective ease of falling back to sleep, and sleep quality were secondary efficacy variables that were determined by the post-sleep questionnaire.

10.2.7.3.6 Statistical analysis

The intent-to-treat population (ITT) was to be defined as all subjects who were randomized and received one dose of study medication. This population was the primary one for analysis of safety, efficacy and residual pharmacological effects. The analyses were to be done on observed data collected at screening, day-1 check-in and day-2 check-out.

In the analysis of the primary efficacy variable, latency to persistent sleep, comparisons of each active treatment arm and placebo were to be made using Dunnett's t-tests and least squares means obtained from a two-way ANOVA with center and treatment as factors. The mixed model procedure (PROC MIXED) with all effects fixed and Type III sums of squares were to be used to generate the ANOVA results.

10.2.7.3.7 Protocol amendment

The protocol amendment, dated 14 April 2003, made the following substantive changes in addition to minor administrative changes:

- Added updated references
- Clarified subjective variables
- Incorporated preliminary information from potential drug interaction studies
- Corrected the urine drug screen to remove cotinine
- Requested the maintenance of a temperature log for the study medication storage area
- Clarified the serious adverse event reporting process
- Clarified the planned display of adverse events
- Clarified definitions of PSG parameters to make it clear that data to the end of the recording period would be scored not until the end of sleep
- Added a definition for wake time after persistent sleep
- Clarified that the central reader would evaluate and score all PSG data

10.2.7.4 Study results

10.2.7.4.1 Trial characteristics

This study began screening subjects on 26 December 2002. The last patient completed the study on 09 May 2003. A total of 289 patients were enrolled and randomized into the intent-to-treat population; the per-protocol population had 276 subjects.

10.2.7.4.2 Demographics

Table 70: Demographics for study TL-023

	Placebo N=97	**TAK-375 8 mg N=98**	**TAK-375 16 mg N=94**
Age (years) Mean (SD)	29.8 (9.71)	28.5 (9.07%)	28.1 (9.4)
Sex			
Male	40 (41%)	43 (44%)	45 (48%)
Female	57 (59%)	55 (56%)	49 (52%)
Ethnicity			
White	64 (66%)	60 (61%)	69 (73%)
Black	4 (4%)	10 (10%)	4 (4%)
Hispanic	21 (22%)	22 (22%)	19 (20%)
Asian	7 (7%)	5 (5%)	2 (2%)
Other	1 (1%)	1 (1%)	0

(modification of table 10.a from the study report)

There was one patient, who had been randomized to the placebo arm, who discontinued early.

There were no statistically significant differences between the groups in the level of habitual tobacco, alcohol or caffeine use. The Epworth sleepiness scale was used at screening: there were no statistically significant differences seen between the treatment groups. The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, quality of usual sleep and decreased ability to function associated with sleep.

10.2.7.4.3 Protocol violations

The majority of the subjects had protocol deviations reported by the investigators, 190 out of the 289 subjects.

Table 71:

	Treatment			
Deviation Category	**Placebo n=97**	**Ramelteon 8 mg n=98**	**Ramelteon 16 mg n=94**	**Total N=289**
Number of subjects with any deviations	63	64	63	190
Study medication	4	1	1	6
Visit date window	3	3	3	9
Prohibited medications	3	2	2	7
Other	63	61	59	183

Source: Table 14.1.1.3.
(modification of table 10.c from the study report)

The prohibited medications taken prior to Day 1 were:

- Dayquil: one subject-placebo group
- Ultracet: one subject-placebo group
- Nyquil: one subject-8 mg group
- Xenadrin: one subject-16 mg group
- Benedryl: one subject-16 mg group
- Vicodin: one subject-16 mg group

The prohibited medications detected on Day 1 were:

- Propoxyphene: one subject-placebo group
- Cocaine : one subject-8 mg group

The sponsor's review of the data detected 24 protocol deviations. One subject in the 8 mg group and 2 subjects in the 16 mg group did not meet the inclusion criteria that required subjects to sleep 6.5 to 8 hours per night and have a subjective sleep latency of 30 minutes or less.

Table 72:

Deviation Category	Placebo n=97	Ramelteon 8 mg n=98	Ramelteon 16 mg n=94
Number of subjects with any deviations	1	12	11
Violated inclusion/exclusion criteria	0	7	6
Received prohibited medications	1	6	5
Received wrong treatment or dose	0	0	0

(modification of table 10c)

10.2.7.4.4 Efficacy endpoints

The number of patients analyzed was 288 not 289 since one subject (#12549/231009, 16 mg group) did not have PSG measurements. The PP population excluded 13 patients.

Primary endpoint

Analysis of the data from the ITT population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.015), but when considered individually, the results from the 8 mg group were significant (p=0.004) while those from the 16 mg were not (p=0.065).

Table 73: LPS-ITT population

	Placebo (n=97)	Tak-375 8 mg (n=98)	Tak-375 16 mg (n=93)
LPS (minutes)			
LS mean (SE) LSM difference from placebo (SE) (95% CI)	19.7 (1.87)	12.2 (1.88) -7.6 (2.62) (-12.7, -2.4)	14.8 (1.93) -4.9 (2.65) (-10.1, 0.3)

(study report table 11.a)

Log transformation and nonparametric analyses were performed as confirmatory analyses. The former analysis confirmed the primary analysis. The latter did not show statistically significant treatment differences, although the trend reflected the primary analysis.

Analysis of the data from the PP population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.020), but when considered individually, the results from the 8 mg group were significant (p=0.006) while those from the 16 mg were not (p=0.098).

Secondary endpoints

- Total Sleep Time (TST)

Analysis of the data from the ITT population revealed a statistically significant treatment effect for both groups when compared to placebo (p=0.024): TAK-357 8-mg group (p=0.009); TAK-375 16-mg group (p=0.043).

Analysis of the data from the PP population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.044), but when considered individually, the results from the 8 mg group were significant (p=0.017) while those from the 16 mg were not (p=0.070).

- Sleep Efficiency (SE)

Analysis of the data from the ITT population revealed a statistically significant treatment effect for both groups when compared to placebo (p=0.029): TAK-357 8-mg group (p=0.011); TAK-375 16-mg group (p=0.058).

- Wake time after sleep onset (WASO)

Upon analysis of the results from the ITT population, no overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.562) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 8-mg group (p=0.283); TAK-375 16-mg group (p=0.592).

- Number of awakenings

Upon analysis of the results from the ITT population, no overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.667) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 8-mg group (p=0.408); TAK-375 16-mg group (p=0.473).

- Subjective sleep latency (sSL)

Upon analysis of the results from the ITT population, no overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.530) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 8-mg group (p=0.266); TAK-375 16-mg group (p=0.676).

- Subjective total sleep time (sTST)

Upon analysis of the results from the ITT population, no overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.289) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 8-mg group (p=0.154); TAK-375 16-mg group (p=0.883).

- Subjective sleep quality (sSQ)

Upon analysis of the results from the ITT population, no overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.614) nor was a statistically significant effect seen when the groups were considered individually: TAK-357 8-mg group (p=0.428); TAK-375 16-mg group (p=0.916).

10.2.7.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.7.5 Reviewer's Summary

This study demonstrated a statistically significant difference in objectively measured LPS for the 8 mg dose as compared to placebo, which supports the idea that this drug may have an effect on sleep initiation in transient insomnia. An increase in dose from 8mg to 16 mg did not appear to provide added benefit.

It is of interest to note that the subjective sleep quality results in the 8 mg group did not reflect the expected improvement despite statistically demonstrated improvement in objective LPS, and objective TST.

The increase in objectively measured LPS, for the 8 mg group, led to both an increase in objectively measured TST and improved SE. Since the latter measures are a reflection of the change in LPS, it would be misleading to imply that they are separate drug benefits.

10.2.8 Study TL025: A Phase III randomized, double-blind, placebo-controlled, outpatient safety and efficacy study in elderly patients with chronic insomnia

10.2.8.1 Objectives

To assess the safety and efficacy of TAK-375 at doses of 4 and 8 milligrams, as compared to placebo, on subjective sleep latency.

10.2.8.2 Study design

A randomized, double-blind, placebo-controlled, fixed-dose, parallel group multi-center 35-nights outpatient study in elderly patients with chronic insomnia

10.2.8.3 Study population and procedures

10.2.8.3.1 Study duration

Each participant was to be studied for 49 days, comprised of a 7 night single-blind placebo run-in, 35 nights of double-blind treatment followed by 7 nights of placebo run-out.

10.2.8.3.2 Entry criteria

Inclusion criteria

1. Healthy male or post-menopausal females ≥65 years old
2. Chronic insomnia, as defined by DSM IV-TR, for at least 3 months and a history of daytime complaints associated with disturbed sleep
3. A subjective sleep latency (sSL) greater than or equal to 45 minutes and a subjective total sleep time (sTST) less than or equal to 6.5 hours/night for at least 3 nights during the week of the lead-in period, based on subject diary
4. Habitual bedtime between 8:30 PM and 12 AM
5. Body mass index (BMI) between 18 and 34, inclusive
6. Able to write, read and speak English
7. Capable of understanding and willing to comply with the protocol
8. Signed informed consent document at screening

Exclusion criteria

1. Known hypersensitivity to TAK-375 or related compounds including melatonin
2. Previous participation in a study involving TAK-375
3. Use of any other investigational drug within 30 days or 5 half-lives prior to the first day of single-blind study medication, whichever was longer
4. Sleep schedule changes required by employment within 3 months prior to the first day of single-blind study medication
5. Had flown across greater than 3 time zones within the 7 days prior to screening

6. Participation in a weight-loss program or alteration of exercise routine within 30 days prior to the first day of single-blind study medication
7. History of COPD, seizures, sleep apnea, restless leg syndrome, schizophrenia, bipolar disorder, cognitive disorder or mental retardation
8. History of psychiatric disorder (including anxiety or depression) within the previous 12 months
9. History of drug addiction or drug abuse within the past 12 months
10. History of alcohol abuse within past 12 months, as defined in the DSM-IV-TR and/or regularly consumes 4 or more alcoholic drinks/day
11. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease, unless currently controlled and stable with protocol allowed medication 30 days prior to the first day of single-blind study medication
12. Use of tobacco products during nightly awakenings
13. Use of melatonin, or other drugs/supplements known to affect sleep/wake function within 5 days prior to the first night of single-blind study medication
14. Use of CNS-active drugs within 3 weeks (or 5 half-lives of the drug, whichever is longer) of single blind medication. The medications in question must not have been used to treat psychiatric diseases.
15. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the three weeks prior to screening.
16. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
17. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody (only IgM was exclusionary) or HCV antibodies
18. Any additional conditions that in the investigator's opinion would affect sleep-wake function, prohibit the subject from completing the study or not be in the best interest of the subject

10.2.8.3.3 Study medications

- TAK-375 4 mg
- TAK-375 8 mg
- Placebo

Prohibited concurrent therapy

The use of the following medications was prohibited beginning 3 weeks prior to the first day single-blind study medication and during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, CNS active drugs (including herbal preparations with CNS effects), narcotic analgesics and all beta

blockers, St. John's wort, kava-kava, gingko biloba, any other supplements, OTC or prescription medications that may interfere with the evaluation of the study medication.

Medications prohibited within 5 days prior to first day of single-blind study medication and during the study included melatonin or other drugs or supplements known to affect sleep/wake function.

10.2.8.3.4 Study procedures

Initial screening period including PSG (Day -21 to Day -9)
The initial screening was to consist of a physical examination including vital signs, medical history including sleep history, laboratory testing and a 12-lead ECG.

Single-blind placebo lead-in period (Day-7 to Day -1)
Baseline symptoms were to be assessed through review of daily diary data obtained while patient was on placebo.

At the end of this period, patients were to be randomized into one of the three treatment arms: ramelteon 4 mg, ramelteon 8 mg or placebo.

Double-blind treatment period (Day 1 to Day 35)
Patients were to take the study medication nightly at home. Throughout the course of the study, subjects were to be asked to maintain subject diaries and return for weekly clinic visits at which the diary entries, the concomitant medication history and any adverse events would be reviewed. The diaries were to be used to collect information on study medication compliance, bedtime, time to sleep onset, total sleep time, sleep quality, number of awakenings and ease of falling back to sleep.

At each visit, patients would complete the Tyrer benzodiazepine withdrawal symptom questionnaire (BWSQ). The clinician would provide a clinical global impression.

A 12-lead ECG was to be done at the Week 5 Visit, i.e. the completion of the double-blind period and beginning of the single-blind run-out period.

Single-blind run-in period (Day 43)
Once the patients had completed 35 days of double blind treatment, they were to receive single-blind placebo medication. This single-blind run-out period was to be used to evaluate for rebound insomnia and or withdrawal effects.

Final visit (Day 43)
The final evaluations, including a 12-lead ECG, were to take place on Day 43.

10.2.8.3.5 Efficacy parameters

Primary efficacy variable

- Average subjective sleep latency, per subject diary, from nights 1 through 7 of double-blind treatment

Secondary efficacy variables

- Average sleep latency over the week preceding the Day 15, Day 22, Day 29 and Day 36 visits
- Total sleep time
- Sleep quality
- Number of awakenings
- Ease of falling back to sleep after awakening
- Clinician's Clinical Global Impression (CGI)

10.2.8.3.6 Statistical analysis

The intent-to-treat (ITT) population was the population to be used for analysis of efficacy and safety. While the ITT population was to consist of all randomized subjects who received at least one dose of double-blind study medication, in practice the analyses for a given variable would only include those patients who had a measurement for that variable.

The efficacy analysis was to be based on LOCF data, though the observed data would also be presented. ANOVA with treatment and pooled center as factors was to be used to evaluate baseline characteristics of the variables. Safety analyses were to be based upon observed data.

Comparisons between treatment groups was to be made using t-tests with least square means and standard errors obtained from the following ANCOVA model:

parameter=baseline+center+treatment

The mixed model procedure (PROC MIXED) with center and treatment effects fixed was to be applied. Type III sums of squares was to be used to generate the ANCOVA results. Since the primary efficacy analysis time point was week 1, the average of the available observations for Week 1 was to be analyzed. Maintenance of efficacy was to be assessed at week 3 and 5 using a sequential testing procedure.

Weekly time windows, i.e. nights 1-7, 8-14, 15-21, 22-28, 29-last dose of double-blind study medication, were defined for the collection of subjective assessment variables. The average of the available data for a weekly time window was to be analyzed. When no data was available for a time window, the values from the last available time window would be carried forward. The average of the available observations from the single-blind lead in period was to be considered the baseline. Observations from each day of the single-blind run-out period were to be used to assess rebound insomnia.

No interim analysis was planned.

10.2.8.3.7 Protocol amendments and administrative changes

The only protocol amendment was dated 20 January 2003. In addition to minor administrative changes, the following modifications were made:

- Clarified the washout period for exclusionary medications was within one week or 5 half-lives whichever was longer
- Incorporated preliminary information from potential drug interaction studies
- Requested the maintenance of a temperature log for the study medication storage area
- Clarified fasting requirements prior to laboratory sample collection
- Clarified the SAE reporting process
- Clarified the planned analysis for the BWSQ, with withdrawal to be calculated as change from the last day on double-blind treatment to the placebo run-out score
- Clarified the planned display of adverse events
- Corrected minor administrative discrepancies e.g. titles, spelling errors

The first of two administrative changes was made on 5 May 2003. This change added the Canadian Health authority and other regulatory bodies in addition to correcting administrative discrepancies.

The second of two administrative changes was made on 23 June 2003. This change re-inserted a paragraph that had been inadvertently deleted in the submission incorporating administrative change 1.

10.2.8.3.8 Changes to the planned statistical analysis

The sponsor reported that the statistical analysis plan was modified to account for problems with data collection which were discovered during the study.

The protocol specified weekly time windows as nights 1-7, 8-14, 15-21, 22-28 and 29-last dose of double-blind study medication and that the average of the non-missing data for a given weekly time window was to be analyzed.

"Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. Because the dates recorded on the diary CRFs were deemed to be potentially inaccurate, the data recorded on the CRFs were applied to the visit label on the CRF. For example all data recorded on the CRF for Week 1 were analyzed for that visit. No recorded dates were checked. The SAP that was finalized for the study, prior to unblinding, included these changes. (final study report, section 9.8)"

10.2.8.4 Study results

10.2.8.4.1 Trial characteristics

This study began on 30 December 2002 and ended on 23 January 2004. A total of 136 study sites enrolled patients.

The plan was to enroll 810 patients. The final ITT and safety population had 829 subjects. The per-protocol population (PP) had 670 patients.

10.2.8.4.2 Demographics

Table 74: Demographics for study PNFP-025

	Placebo (PBO) N=274	**Ramelteon 4 mg N=281**	**Ramelteon 8 mg N=274**
Age (years)			
Mean (SD)	72.4 (5.94)	72.1 (6.03)	72.6 (5.88)
Sex			
Male	108 (39%)	110 (39%)	123 (45%)
Female	166 (61%)	171 (61%)	151 (55%)
Ethnicity			
White	251 (92%)	252 (90%)	241 (88%)
Black	9 (3%)	14 (5%)	17 (6%)
Hispanic	8 (3%)	12 (4%)	11 (4%)
Asian	3 (1%)	0	3 (1%)
Native American	1 (<1%)	3 (1%)	0
Other	2 (<1%)	0	2 (<1%)

(modification of table 10b from the final study report)

A total of 136 patients did not complete the study:

- 29 patients withdrew due to adverse events
  - 8 in the placebo group
  - 9 in the 4 milligram group
  - 7 in the 8 milligram group
- 40 due to lack of efficacy
  - 17 in the placebo group
  - 14 in the 4 milligram group
  - 9 in the 8 milligram group
- 39 due to protocol deviations
  - 12 in the placebo group
  - 16 in the 4 milligram group
  - 11 in the 8 milligram group
- 21 withdrew consent
  - 7 in the placebo group
  - 7 in the 4 milligram group
  - 7 in the 8 milligram group
- 1 was lost to follow-up in the 4 mg group
- 2 were withdrawn due to investigator's discretion
  - 1 in the placebo group
  - 1 in the 4 milligram group
- 9 due to "other" reasons
  - 4 in the placebo group
  - 2 in the 4 milligram group
  - 3 in the 8 milligram group

There were no statistically significant differences at baseline among the treatment groups for the demographic characteristics. There were no statistically significant differences between the groups in the level of habitual tobacco, alcohol or caffeine use. A higher proportion of nonsmokers and a lower proportion of current smokers was found in the placebo group as compared to the ramelteon groups, the difference was statistically significant with a p-value=0.028. There were no statistically significant differences seen in the treatment groups for any relevant sleep parameter. There were no significant differences between the treatment groups when the use of prior and /or concomitant medications was reviewed.

10.2.8.4.3 Protocol violations

The majority of the subjects had protocol deviations reported by the investigators, 480 out of the 829 subjects. The sponsor listed the following as examples of the deviations captured under the category "other": time to sleep earlier or later than specified by the protocol, incomplete recording of diary entries, omission of fasting prior to blood draw or CGI completed by an alternate rater.

Table 75:

	Treatment			
Deviation Category	**Placebo n=274**	**Ramelteon 4 mg n=281**	**Ramelteon 8 mg n=274**	**Total N=829**
Number of subjects with any deviations	159	158	163	480
Study medication	38	34	43	115
Visit date window	52	47	41	140
Prohibited medications	22	24	22	68
Other	109	117	117	343

Source: Table 14.1.1.3.
(table 10.c from the study report)

The sponsor's review of the data detected 233 protocol deviations. Slightly more than 10% of the patients (n=97) did not meet the inclusion criteria that required subjects to have a subjective sleep latency of 45 minutes or moer and a subjective total sleep time less than or equal to 6.5 hours.

Table 76:

Deviation Category	**Placebo n=274**	**Ramelteon 4 mg n=281**	**Ramelteon 8 mg n=274**
Number of subjects with any deviations	73	86	74
Violated inclusion/exclusion criteria	43	50	43
Received prohibited medications	32	36	37
Double blind study medication compliance below 70%	0	0	0

(modification of study report table 10d)

The sponsor reports that "site number 20759 did not comply with critical procedures of the study and therefore was not included in the PP population."
[*Reviewer's note: The sponsor was contacted, via email, on May 24 2005 to ask for further information on this violation.*]

The sponsor also reported the following database errors which were not corrected:
Placebo Group:

- Subject 10566/252531 had a Grade I/IV apical systolic murmur recorded instead of a Grade I/IV systolic ejection murmur recorded at the final visit.
- Subject 20381/251438 did not meet all inclusion criteria at screening
- Subject 12726/251045 had an incorrect duration recorded in diary item #4

Ramelteon 4 mg group

- Subject 12726/251043 had two occasions where study medication was not taken that were not recorded
- Subject 21193/252633 had abnormal hearing loss at the screening visit which was not recorded
- Subject 10566/251551 was studied despite clinically significant abnormal creatinine and albumin at screening
- Subject 12726/251047 had an incorrect QRS value recorded at screening

10.2.8.4.4 Efficacy endpoints

In all cases the results from the analyses of the PP population agreed with the findings from the analyses of the ITT population, so the results from the PP population analyses are not presented here.

Primary endpoint

The primary endpoint for this study was average subjective sleep latency, per subject diary, from nights 1 through 7 of double-blind treatment

Analysis of the data from the ITT population revealed a statistically significant treatment effect overall when ramelteon was compared to placebo (p=0.009), as well as when considered individually: 4 mg group (p=0.008), 8 mg group (p=0.008).

Table 77: sSL-ITT population (LOCF data)

	Placebo (n=274)	Tak-375 4 mg (n=280)	Tak-375 8 mg (n=272)
sSL (minutes)			
LS mean (SE) LSM difference from placebo (SE) (95% CI)	78.5 (2.24)	70.2 (2.21) -8.3 (3.10) (-14.4, -2.2)	70.2 (2.24) -8.3 (3.12) (-14.5, -2.2)

(study report table 11.a)

Log transformation and nonparametric analyses were performed as confirmatory analyses. The former analysis confirmed the primary analysis. The latter did not show

statistically significant treatment differences, although the trend reflected the primary analysis.

Secondary endpoints

- Average subjective sleep latency over the week preceding the Day 15 visit
  When the least square means were calculated, the 4 mg group showed a difference from placebo of -4.9, while the 8 mg group showed a difference of -9.2.

- Average subjective sleep latency over the week preceding the Day 22 visit
  When the least square means were calculated, the 4 mg group showed a difference from placebo of -4.5 (p=0.142), while the 8 mg group showed a difference of -9.2 (0.003).

- Average subjective sleep latency over the week preceding the Day 29 visit
  When the least square means were calculated, the 4 mg group showed a difference from placebo of -1.7, while the 8 mg group showed a difference of -7.5.

- Average subjective sleep latency over the week preceding the Day 36 visit
  When the least square means were calculated, the 4 mg group showed a difference from placebo of -7.1(p=0.028), while the 8 mg group showed a difference of -12.8 (p<0.001).

- Subjective total sleep time (sTST)
  Upon analysis of the results from the ITT population in week 1, an overall statistically significant treatment effect was seen when active drug was compared to placebo (p=0.015) and when the 4 mg group was considered individually (p=0.004). This effect was not seen when the 8 mg group was considered individually (p=0.055).

  By week 3, only the results from the 4 mg were statistically significant.

  By week 5 neither group produced statistically significant results.

- Subjective sleep quality (sSQ)
  Upon analysis of the results from the ITT population, no statistically significant treatment effect was seen when active drug was compared to placebo.

- Ease of falling back to sleep after awakening
  Upon analysis of the results from the ITT population, no statistically significant treatment effect was seen when active drug was compared to placebo.

- Number of awakenings
  Upon analysis of the results from the ITT population, no statistically significant treatment effect was seen when active drug was compared to placebo.

- Clinician's Clinical Global Impression (CGI)
  Upon analysis of the results from the ITT population, no statistically significant treatment effect was seen when active drug was compared to placebo.

10.2.8.4.5 Safety

The safety data, including residual pharmacological effects, have been discussed in section 7 of this review.

10.2.8.5 Reviewer's Summary

This study demonstrated an overall effect as well as an individual effect of the 4 mg and 8 mg doses at week 1. This effect was only present at the 8 mg dose by weeks 3 and 5.

It is of interest that the subjective total sleep time did not mirror the improvement in subjective time to sleep onset. Upon analysis of the former parameter, a treatment effect was seen in the 4 mg group during weeks 1 and 3. An effect was never noted in the 8 mg group.

At no time and on neither dose were statistically significant improvements in sleep quality noted.

I note that this study did not incorporate the DSST or memory recall tests so we do not have information on next-day residual effects from this trial.

10.2.9 Study TL032: A Phase III safety study to evaluate the long-term effects of TAK-375 on endocrine function in adult subjects with chronic insomnia

10.2.9.1 Objectives

To determine if long-term administration of TAK-375 16 mg has an effect on endocrine function
To confirm the safety profile of long-term dosing of TAK-375 16 mg in subjects with chronic insomnia

10.2.9.2 Study design

A randomized, double-blind, placebo-controlled, parallel group multi-center study in healthy adult patients with chronic insomnia

10.2.9.3 Study population and procedures

10.2.9.3.1 Study duration

6 months per study participant

10.2.9.3.2 Entry criteria

Inclusion criteria

1. Healthy adults ≥18 and ≤45 years old
2. Women of child-bearing potential must use barrier methods of contraception and/or intrauterine devices for the duration of the study. Hormonal contraceptives of any type, abstinence, vasectomy and/or partner sterility were not to be considered acceptable methods of contraception.
3. Women must have regular menstrual cycles
4. Chronic insomnia as defined by DSM IV and a history of daytime complaints associated with disturbed sleep) for at least 3 months
5. sSL ≥45 minutes and a sTST ≤ 6.5 hours/night for at least 3 nights out of 1 week
6. Habitual time of awakening between 5 AM and 10 AM
7. Habitual bedtime between 8:30 PM and 12 AM
8. Subject with baseline values of melatonin, cortisol, LH, FSH, estradiol, testosterone, prolactin, ACTH, TSH, T3 and T4 within normal range.
9. Body Mass Index between 18 and 30 inclusive
10. Capable of understanding and complying with the protocol
11. Signed informed consent document at screening
12. English fluency

Exclusion criteria

1. Pregnancy or lactation
2. Known hypersensitivity to TAK-375 or related compounds including melatonin

3. Previous participation in a study of TAK-375
4. Use of any other investigational drug within 30 days or 5 half-lives, whichever was longer
5. Sleep schedule changes required by employment within 3 months preceding Day 1
6. Had flown across greater than 3 time zones within the past 7 days
7. Participation in a weight-loss program or alteration of exercise routine within 30 days preceding Day 1
8. History of seizures, sleep apnea, COPD, restless leg syndrome, schizophrenia, bipolar disorder mental retardation or cognitive disorder
9. History of psychiatric disorder (including anxiety or depression) within the past 12 months
10. History of drug addiction or drug abuse within the past 12 months
11. History of alcohol abuse within past 12 months and/or regularly consumes 4 or more alcoholic drinks/day
12. Current significant neurological (including psychiatric and cognitive), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological or metabolic disease unless currently controlled and stable with protocol allowed medication 30 days prior to Day 1
13. Use of tobacco products during nightly awakenings.
14. Use of melatonin or other drug/supplements known to affect sleep/wake function within 1 week (or 5 drug half-lives whichever is longer) prior to Day 1
15. Use of any central nervous system medication with one week or 5 half-lives of the drug which ever is longer prior to Day 1. These medications must not have been used to treat psychiatric conditions.
16. Intent to use any disallowed, prescription or OTC medication during the study that could interfere with the evaluation of study medication. The subject must have reported all prescription and OTC medications taken in the 3 weeks prior to screening.
17. Clinically important abnormal findings as determined by a medical history, physical examination, ECG, or clinical laboratory tests as determined by the investigator. Subjects with clinically significant abnormal levels who were being considered for the study must have been approved by both TPNA and the principal investigator
18. A positive test for hepatitis panel including anti-HAV antibody (only IgM was exclusionary), anti-HBs (except in subjects who had received HBV vaccination), HBV surface antigen, HBV core antibody or HCV antibodies
19. Any significant endocrine pathology based on borderline laboratory results
20. Any additional conditions that in the investigator's opinion would a) affect endocrine function, b) prohibit the subject from completing the study or c)not be in the best interest of the subject

10.2.9.3.3 Study medications

- TAK-375 16 mg
- Placebo

Prohibited concurrent therapy
The use of the following medications was prohibited beginning 1 week (or 5 half-lives prior to Day 1 of study medication as well as during the study: anxiolytics, hypnotics, antidepressants, anticonvulsants, sedating H1 antihistamines, systemic steroids, respiratory stimulants/decongestants, OTC and prescription stimulants, OTC and prescription diet aids, herbal preparations with CNS effects, narcotic analgesics and all beta blockers St. John's wort, kava-kava, gingko biloba, melatonin, any other supplements, OTC or prescription medications that may interfere with the evaluation of the study medication.

All hormonal medications (prescription or OTC) will be prohibited including hormonal replacement therapy, hormonal contraceptives, and dietary and athletic supplements.

10.2.9.3.4 Study procedures

As part of screening, the subjects were to have a physical examination, laboratory testing including evaluation of baseline endocrine values and a 12-lead electrocardiogram. Pre-menopausal women were to provide a menstrual history.

All subjects who met the screening criteria and had normal examinations including laboratory values and electrocardiogram results were to be randomized (1:1) to one of two treatment arms: placebo or 16 mg of TAK-375.

Subjects were asked to take a single dose of TAK-375 or placebo nightly. Female participants were asked to complete a menstrual diary over the six months.

During the six month study period, subjects were to return monthly for safety assessments and laboratory tests, along with investigator evaluation of adverse events, concomitant medications, and menstrual diaries.

Fasting morning blood draws for endocrine function tests were to be drawn within 3 hours of habitual morning awakening at the following visits: at screening, on Day 1, months 1, 2, 3, 4, 5, 6, at follow-up.

Adrenocorticotrophic hormone stimulation testing was to be conducted in a subset of patients 50 patients, 1:1 placebo:active, at the Day 1 and Month 6 visits. The LH surge testing was to be done using a home test kit with urine provided by the (female) subjects on the appropriate days.

All study medications were to be discontinued at the end of the 6 month treatment period. After a two week washout period, subjects were to return for a final overall assessment including endocrine function tests.

10.2.9.3.5 Endocrine parameters

The following (fasting) levels were to be drawn during screening and then monthly:
Prolactin, ACTH, Cortisol, T3, T4 and free T4, TSH, LH, FSH , estradiol (females), free and total testosterone (males)

LH surge was to be monitored in months 1-6
Females were to keep monthly menstrual diaries.

10.2.9.3.6 Safety parameters

Subjects were to be monitored for adverse events throughout the study period. Spontaneous reports of AEs were to be collected up to 30 days after the administration of the last dose of study medication.

Cortisol abnormalities

The protocol called for special handling of potential cortisol abnormalities. AM cortisol values in the range of 7.5-10 microgram/dl will be evaluated and treated as an adrenal adverse event and recorded on the appropriate CRF. In addition, the investigator was to conduct and ACTH stimulation test. In the event of a positive test indicative of adrenal insufficiency, the investigator was to report said event as "a significant adrenal adverse event." Any AM cortisol values less than 7.5 micrograms/dl were to be reported as a significant adrenal adverse event, recorded on the appropriate CRF and reported to TPNA.

Testosterone abnormalities

Patients found to have new abnormalities of either free or total testosterone were to have a reevaluation of testosterone as well as a simultaneous gonadotrophin determination as soon as possible after the initial abnormal finding.

10.2.9.3.7 Statistical analysis

The sponsor planned to enroll 60 patients (1:1::male:female) in each treatment arm, with randomized treatment assignments stratified by gender.

The intent-to-treat population consisted of all randomized subjects who received at least on e dose of double-blind medication. This was to be the primary population for safety analysis.

The sponsor planned to use a repeated measures analysis for change from baseline to compare the overall effects on endocrine factors between the ramelteon and the placebo groups. The mean changes from baseline in the two treatment arms was to be calculated at each visit. The mean changes from baseline after the 2-week washout period will also be compared for ramelteon and placebo. The percentage of subjects in each treatment arm for whom the endocrine measure is below the lower limit of the normal range was to be tabulated and compared between treatment groups at each visit, with the results at week 24 designated as being of primary importance.

The primary measure of safety was to be the change from baseline in total thyroxine. Comparisons were to be made between treatment arms using a t-test with least squares means and standard errors obtained from a full multivariate normal model, where parameter is change from baseline in total thyroxine and baseline is the measure of total thyroxine at baseline:

Parameter=baseline + center + gender + period + treatment + random error

The mixed model procedure with unstructured covariance structure for the random errors was to be applied. A F-test with type III sum of squares was to be used to test significance of each of the fixed effects in the model.
The second safety endocrine measure, total testosterone in males, was to be analyzed using the same methods described above with the omission of gender as a factor in the model.

10.2.9.3.8 Protocol amendments

The first protocol amendment was dated 17 February 2003.
In this amendment, the sponsor did the following:

- Corrected administrative discrepancies and typographical errors
- Added inclusion criteria
  - Male subjects had to have testosterone values within a normal range
  - Female subjects had to have estradiol values within a normal range
- Clarified that cosyntrophin would be supplied by TPNA
- Changed the requirement for an ACTH stimulation test to be performed in a subset of patients to require that it be performed in all patients
- Clarified the compensation and treatment for injury process in the sample informed consent
- Added language to the informed consent clarifying the requirement procedures and associated risks of the adrenocorticotrophin stimulation test
- Added both a menstrual diary and the adrenocorticotrophin hormone stimulation test as appendices to the protocol
- Increased the number of clinical trial sites participating in the study

The second protocol amendment was dated 05 May 2003.
In this amendment, the sponsor did the following:

- Corrected administrative discrepancies and typographical errors
- Updated information from two recently completed animal carcinogenicity studies
- Added an exclusionary value for serum cortisol $\leq$ 7.0 micrograms/deciliter at screening
- Adjusted the threshold values for the monitoring and reporting of cortisol values due to the lower limit of normal for the cortisol assay being utilized by the central laboratory
- Specified that the fasting laboratory samples were not to be drawn after 10 am
- Added language to the informed consent template clarifying the requirements fro the ACTH stimulation test
  - Values less than the gender-specific lower limit of normal were to be treated as adrenal adverse events
  - Values under 3 micrograms/deciliter were to result in an ACTH stimulation test
- Added language to comply with the requirements of the health Insurance Portability and Accountability Act (HIPAA)

The second protocol amendment was dated 23 October 2003.
In this amendment, the sponsor did the following:

- Corrected administrative discrepancies and typographical errors
- Elaborated upon items in the inclusion/exclusion criteria

10.2.9.4 Study results

10.2.9.4.1 Trial characteristics

This study began on 30 January 2003 and ended on 1 July 2004. A total of 23 study sites, all of which were in the United States of America, enrolled patients. The plan was to enroll 120 patients. The final ITT and safety population had 122 subjects.

10.2.9.4.2 Demographics

Table 78: Demographics for study TL032

	Placebo (PBO) N=287	**Ramelteon 16 mg N=284**
Age (years)		
Mean (SD)	34.1 (7.30)	34.5 (8.07)
Sex		
Male	30 (46.2%)	23 (40.4%)
Female	35 (53.8%)	34 (59.6%)
Ethnicity		
White	49 (75.4%)	42 (73.7%)
Black	5 (7.7%)	5 (8.8%)
Hispanic	9 (13.8%)	9 (15.8%)
Asian	1 (1.5%)	0
Native American	0	0
Other	1 (1.5%)	1 (1.8%)

A total of 56 patients did not complete the study:

- 8 patients withdrew due to adverse events
  - 2 in the placebo group
  - 6 in the 16 milligram group
- 10 due to lack of efficacy
  - 5 in the placebo group
  - 5 in the 16 milligram group
- 10 due to protocol deviations
  - 5 in the placebo group
  - 5 in the 16 milligram group
- 14 withdrew consent
  - 4 in the placebo group
  - 10 in the 16 milligram group
- 10 were lost to follow-up
  - 5 in the placebo group
  - 5 in the 16 milligram group
- 1 in the 16 milligram group due to "other" reasons
- 2, in the placebo group, were terminated at the investigator's discretion
- 1 in the placebo group was discontinued due to pregnancy

There were no statistically significant differences between the groups in the level of habitual tobacco, or alcohol use. The proportion of caffeine users was higher in the placebo group (84.6%0 than in the ramelteon group (68.4%). The sleep history for each participant was taken at screening with an update done at Day 1 check-in: there were no statistically significant differences seen in the treatment groups for any relevant characteristic including usual time to fall asleep, usual hours of sleep time, quality of usual sleep and decreased ability to function associated with sleep. There were no significant differences between the treatment groups when the use of prior and /or concomitant medications was reviewed.

10.2.9.4.3 Protocol violations

Protocol deviations were reported for a total of 113 subjects in the intent-to-treat population: 58/65 in the placebo group; 55/57 in the ramelteon group. The usual deviations were deviations in visit date windows, use of prohibited medications, failure to perform LH surge and ACTH testing at the specified time or at all.

Entry criteria deviations were reported for 56 subjects (34 in the placebo group and 22 in the ramelteon group). The most commonly violated criteria were exclusion criterion 14 which related to concomitant medication use and inclusion criterion 11 which specified the baseline serum testosterone level required for study entry. Of the 32 subjects who did not meet exclusion criterion 14, 18 were granted an exemption. The original protocol stated that no medications were permissible during the study. In protocol amendment #3, this criterion was changed to allow subjects to take concomitant medications which had not been specifically excluded. Of the 15 subjects who failed to meet inclusion criterion 11, 13 were granted exemptions. The original protocol stated that men had to have a baseline total testosterone level within reference range for study inclusion. In protocol amendment #3, this criterion was changed to allow subjects with a baseline total testosterone level of at least 150 ng/dL to enter the study.

A total of ten subjects had protocol deviations which led to study discontinuation, five in each treatment group:

- Excluded medication use (3 subjects)
- Failure to meet entry criteria (2 subjects)
- Hormone levels outside the normal range (2 subjects)
- Noncompliance including missing visits (3 subjects)

10.2.9.4.4 Endocrine variables

Primary variable

The primary endpoint for this study was the mean change from baseline in the total T4 value. Overall no statistically significant change was seen in the mean change from baseline nor was a statistically significant change seen in the effect of treatment over time. The ramelteon group did not demonstrate a shift from low/normal to high T4 values at any time during the study.

The sponsor performed log transformation and nonparametric analyses as confirmatory analyses. The results of these analyses corroborated the results of the primary analyses.

Table 79: Mean values at baseline and mean changes from baseline for total T4

Variable	Placebo Group		Ramelteon 16 mg Group		
(reference range)	No. Subjects	LS Mean (SE)	No. Subjects	LS Mean (SE)	P-value (a)
Total T4 (54-161 nmol/L)					
Baseline	65	95.1 (2.15)	56	91.8 (2.33)	0.289
Change from Baseline					
Month 1	55	2.8 (1.82)	46	1.2 (2.00)	0.537
Month 2	51	-0.1 (1.57)	42	0.9 (1.73)	0.655
Month 3	46	3.9 (1.58)	37	2.6 (1.77)	0.599
Month 4	44	-0.6 (1.64)	30	-1.1 (1.98)	0.852
Month 5	43	-0.9 (1.74)	26	-1.1 (2.23)	0.956
Month 6	40	-0.5 (1.81)	24	-3.0 (2.32)	0.377
Follow-up	44	-0.7 (2.13)	33	0.9 (2.44)	0.627
Overall (b)	---	1.1 (1.20)	---	0.1 (1.35)	0.579
					0.970 (c)

Source: Table 14.2.1.2.

--- indicates not applicable.

(a) For comparison of placebo and ramelteon group LS means using Student's t-test.

(b) LS means and P-values for the overall analysis are based on a repeated measures analysis of change from Baseline using an ANCOVA model.

(c) For analysis of treatment-by-period interaction.

(table: 11a from the study report)

Secondary variables

Thyroid axis

Overall no statistically significant change was seen in the mean change from baseline. A statistically significant change was seen in the effect of treatment over time on T3 (p=0.011) overall. One subject in the ramelteon group demonstrated a shift from high/normal to low thyroid axis variables values; this occurred during month 6 and at follow-up.

Adrenal axis

Overall no statistically significant change was seen in the mean change from baseline in ACTH or AM Cortisol nor was a statistically significant change seen in the effect of treatment over time.

Reproductive axis

Overall no statistically significant change was seen in the mean change from baseline in total testosterone, free testosterone, estradiol, FSH, or LH.

There was no statistically significant change seen in the effect of treatment over time in total testosterone, estradiol, FSH, or LH. Evaluations of free testosterone revealed a statistically significant difference in the mean change from baseline during month one; the mean increase from baseline in the ramelteon group was 21.6 pg/mL.

A statistically significant difference in the mean change from baseline for prolactin levels was observed when the active drug group was compared with the placebo arm, p=0.003: mean change for the ramelteon group was +2.9 microgram/L, mean change for the placebo group was -0.6 microgram/L. When evaluated by individual month, the statistically significant differences were noted to occur at Month 1 (mean change for the ramelteon group was +3.7 microgram/L, mean change for the placebo group was -0.8 microgram/L) and Month 4 (mean change for the ramelteon group was +2.5 microgram/L, mean change for the placebo group was -0.1 microgram/L).

While both treatment arms had patients whose prolactin levels switched from low/normal at baseline to high during the study, the proportion of patients doing so was higher in the active treatment arm (10.9% vs. 3.6% at Month 1; 9.5% vs. 3.9% at month 2; 16.7% vs. 9.1% at Month 4.)

Table 80: mean values at baseline and mean changes from baseline for reproductive axis variables

Variable (reference range)	Placebo Group		Ramelteon 16 mg Group		
	No. Subjects	LS Mean (SE)	No. Subjects	LS Mean (SE)	P-value (b)
Prolactin (M: 1.61-18.77 µg/L; F: 1.39-24.20 µg/L) (f)					
Baseline	65	13.6 (0.80)	56	12.7 (0.87)	0.454
Change from Baseline					
Month 1	55	-0.8 (1.02)	46	3.7 (1.12)	0.003
Month 2	51	-0.4 (0.89)	42	2.1 (0.99)	0.054
Month 3	46	-0.3 (1.02)	37	1.3 (1.15)	0.273
Month 4	44	-0.1 (0.76)	30	2.5 (0.92)	0.031
Month 5	43	0.3 (0.86)	26	1.2 (1.10)	0.544
Month 6	40	-1.1 (0.62)	24	-0.9 (0.79)	0.817
Follow-up	44	0.2 (0.87)	33	1.5 (1.01)	0.350
Overall		-0.6 (0.76)	---	2.9 (0.85)	0.003

(modification of table 11e from the study report)

10.2.9.5 Reviewer's Summary

This placebo controlled safety study was primarily notable for the questions raised about ramelteon's effect on prolactin secretion. While causality cannot be definitively determined since other factors are known to increase prolactin secretion, it still gives one pause to realize that the incidence of mild-moderate hyperprolactinemia was higher in the active treatment arm. This is a finding that may best be addressed through further study to document that prolactin levels either normalize over time whilst patients remain on drug or that the levels reliably return to baseline when the drug is withdrawn.

16 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical-_____

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

To:	Division of Anesthetic, Critical Care and Addiction Drug Products
From:	Division of Metabolic and Endocrine Drug Products HFD-510
Reviewing Medical Officer:	Mary H. Parks, MD
Date:	June 17, 2005
Subject:	Consult on NDA 21-782 [ ] (ramelteon) 8 mg tablet

EXECUTIVE SUMMARY

Background

Melatonin is secreted by the pineal gland which is located in the brain behind the third ventricle where it receives input from the suprachiasmatic nucleus. The synthesis and release of melatonin are stimulated by darkness and inhibited by light and is thought to play a role in the biologic regulation of circadian rhythms, sleep, mood, and reproductive function.

Ramelteon is a selective melatonin 1 and 2 receptor agonist under review for an indication to treat insomnia. During clinical development, effects on human testosterone levels were noted in a Phase 1 pharmacokinetic study (EC002) in healthy adult volunteers. In addition, changes in serum testosterone and T4 levels were observed in non-clinical studies involving the rat. Consequently, the Agency required studies to specifically evaluate the effects of ramelteon on the endocrine system.

Clinical Findings

The effects of ramelteon on the endocrine system were evaluated in three separate studies. TL-375-031 was a 4-week, placebo-controlled study with ramelteon 16 mg administered to healthy adult volunteers between 18 and 45 years, inclusive. TL-375-035 was a 6-month, placebo-controlled study with ramelteon 16 mg administered to patients with chronic insomnia who were between 18 and 45 years, inclusive. Finally, TL-375-022 was a long-term, open-label study that evaluated elderly patients (> 65 yrs) treated with ramelteon 8 mg daily and younger patients (< 65 yrs) treated with ramelteon 16 mg daily. While the first two studies provided data from a placebo group, the 4-week study is limited by its short duration of evaluation. An effect of drug treatment on the endocrine system is unlikely to be detected in this one-month study. TL-375-035 and TL-375-022 evaluated the safety of chronic administration of ramelteon in the targeted patient population. The presence of a placebo group in TL-375-035 allowed for some conclusions to be made regarding the possible risks of therapy compared to background risks in the targeted population. While TL-375-022 evaluated both extended use of ramelteon (at least 1 yr) and use in the elderly, the absence of a control group greatly limits any conclusions made regarding the safety finding. As endocrine abnormalities may increase in the aging population, any difference in endocrine laboratory abnormalities noted in the elderly group compared to the younger group may reflect the underlying risks of the older age group and not reflect any consequence of drug therapy.

The thyroid, reproductive, and adrenal axes were evaluated in all three trials. Menstrual diaries were kept in TL-375-035 and TL-375-022, and prolactin levels were measured in TL-375-032 and TL-375-035. Overall, there were no significant differences between placebo and ramelteon for many of the endocrine parameters measured in TL-375-032 and -035. The placebo rates observed in these two trials gave some reassurance that the rates observed in

the uncontrolled, long-term study likely reflected the background risk in the general population and not an effect of drug therapy. Specifically, no consistent abnormalities in testosterone or thyroid levels were observed.

Prolactin levels were increased to a greater extend in the ramelteon group compared to placebo as observed in TL-375-035. This effect appeared to be more pronounced in female patients; however, no patient with marked prolactin elevations reported amenorrhea or menstrual irregularities. Data from 2 non-clinical studies conducted by the applicant demonstrated increased melatonin levels associated with ramelteon administration. Several investigators have shown an association between increased melatonin levels and increased prolactin levels. Consequently, prolactin elevations *may* be a result of drug therapy.

The long-term consequences of chronic hyperprolactinemia include hypogonadism which can lead to infertility and osteopenia/osteoporosis. The applicant did not measure prolactin levels in the open-label extension study; however, there was one case of a prolactinoma reported in a 24 year-old woman treated with ramelteon 16 mg daily who was successfully treated with bromocriptine.

Conclusions and Recommendations

Ramelteon 16 mg administered daily for 6-months in a placebo-controlled study was associated with a significantly greater mean change in prolactin levels than placebo. In this trial, more patients treated with ramelteon had prolactin values > 40 ug/L than placebo. None of these patients had serious clinical consequences resulting from the prolactin elevation (e.g., amenorrhea, decreased libido). Review of published literature has shown an association between melatonin levels and increased prolactin levels. Furthermore, data from two non-clinical studies demonstrating an increase in melatonin levels associated with ramelteon administration suggest a plausible mechanism for prolactin elevation secondary to ramelteon administration.

While the degree of prolactin elevation in this one clinical study was not in the range observed with prolactinomas nor were there any serious adverse events observed as a result of the elevated prolactin levels, the duration of therapy and number of patients evaluated were inadequate to exclude the possibility that ramelteon can be associated with chronic hyperprolactinemia. Persistent hyperprolactinemia, even mild elevations secondary to drug therapy, may have an inhibitory effect on the hypothalamic pulsatile release of gonadotropin-releasing hormone (GnRH) and inhibit the feedback effect of estradiol on luteinizing hormone (LH). Dysregulation of the reproductive axis by persistent hyperprolactinemia may result in hypogonadism which may present as amenorrhea in women and infertility and decreased libido in both genders. Hypogonadism is also a risk factor for osteopenia/osteoporosis. Consequently, it is recommended that patients treated with ramelteon who present with amenorrhea or sexual dysfunction have a prolactin level checked as part of the clinical evaluation. Routine monitoring of prolactin levels while on ramelteon therapy is *not* recommended as prolactin elevation can also occur secondary to non-pathologic etiologies (e.g., stress). Therefore, monitoring is recommended based only on clinical complaints/presentation.

As stated previously, differences in prolactin levels were observed in only one placebo-controlled study which enrolled only 122 patients (randomized 1:1) for 6 months of therapy. Monitoring of prolactin levels in future studies in this clinical development program should be considered to obtain additional data on the extent and persistence of this laboratory abnormality.

TL-375-031

This was a 4-week, randomized, double-blind, placebo-controlled, parallel group study in healthy adult volunteers. The primary objective was to determine if ramelteon 16 mg administered daily for 4 weeks has an effect on endocrine function. The patient population was comprised of healthy men and premenopausal women aged 18 to 45 years, inclusive. Patients had to have had normal baseline endocrine laboratory values.

Endocrine testing included: ACTH; morning cortisol levels; estradiol (women only); FSH and LH; prolactin; free and total testosterone (men only); TSH; T3; free T4; and total T4. The primary measure of outcome was change from Baseline in total T4 at Week 4.

A total of 99 subjects (49 men and 50 women) were randomized to ramelteon (n=50) or placebo (n=49). Of these, 96 subjects completed the study (placebo = 47; ramelteon = 49). All 99 subjects were included in the ITT population. The following table summarizes certain baseline characteristics of the ITT population.

Table 1.

	Placebo n=49	**Ramelteon 16 mg n=50**	**Overall N=99**
Gender, n(%) male female	 24 (49.0) 25 (51.0)	 25 (50.0) 25 (50.0)	 49 (49.5) 50 (50.5)
Age in yrs, mean (SD) Age range in yrs (min-max)	29.1 (7.62) 18-44	30.3 (8.09) 18-44	29.7 (7.84) 18-44

Thyroid Hormone Tests

There were no statistically significant differences in the mean changes from Baseline to Week 4 in T4 (free and total) T3, and TSH levels between the two treatment groups.

Table 2.

Endocrine Measure	**Placebo**		**Ramelteon 16 mg**		**p-value**
	n	Mean (SE)	n	Mean (SE)	
Total T4 (nl range 58-161 nmol/L) baseline chg from baseline @ Wk 4	 49 46	 97.4 (1.94) 1.6 (1.75)	 50 45	 98.8 (1.92) 0.5 (1.79)	 0.595 0.658
Free T4 (nl range 9-24 pmol/L) baseline chg from baseline @ Wk 4	 49 46	 13.0 (0.18) 0.4 (0.22)	 50 45	 12.9 (0.18) 0.6 (0.22)	 0.852 0.504
TSH (nl range 0.32-5 mU/L) baseline chg from baseline @ Wk 4	 49 46	 1.93 (0.152) 0.064 (0.111)	 50 45	 1.908 (0.151) 0.139 (0.114)	 0.919 0.639
T3 (nl range 0.69-2.11 nmol/L) baseline chg from baseline @ Wk 4	 49 46	 1.374 (0.029) -0.064 (0.0257)	 50 45	 1.446 (0.028) -0.007 (0.026)	 0.079 0.124

Three patients (6.1%) in the placebo group (311069, 311013, and 311096) had an abnormal TSH value compared to two (4%) in the ramelteon group (311070, 311077). All five patients had elevated TSH values without free T4

values below the lower limit of normal. One patient in each treatment group had elevated TSH value at Baseline, and one patient in each treatment group had elevated TSH values that persisted throughout the study.

Reproductive Axis

There were no statistically significant differences in the mean changes from Baseline to Week 4 for testosterone (free and total), estradiol, prolactin, FSH, or LH levels between the two treatment groups..

The following table from the applicant's final study report summarizes the changes in reproductive hormones evaluated in study TL-375-031

Table 11.c Mean Reproductive Axis Values at Baseline and Mean Changes from Baseline at Week 4

		Treatment Group				
		Placebo		Ramelteon 16 mg		
Reproductive Axis (Units)	Normal Range	N	Mean Value (SE)	N	Mean Value (SE)	P-value
Total Testosterone (ng/dL) (men only)	M: 350-1030					
Baseline		24	515.0 (25.76)	25	472.2 (25.26)	0.242
Change from Baseline at Week 4		23	-14.7 (17.21)	24	17.6 (16.90)	0.191
Free Testosterone (pg/mL) (men only)	M: 52-280					
Baseline		24	115.0 (5.57)	25	104.3 (5.47)	0.175
Change from Baseline at Week 4		22	-2.3 (6.35)	23	4.2 (6.23)	0.477
Estradiol (a) (women only)	F: 0-1468					
Baseline		25	225.4 (54.54)	25	387.6 (54.54)	0.041
Change from Baseline at Week 4		23	-65.4 (53.35)	20	43.5 (59.84)	0.192
Prolactin (ug/L)	M: 1.61-18.77 F: 1.39-24.2					
Baseline		49	14.245 (0.9383)	50	12.914 (0.9293)	0.316
Change from Baseline at Week 4		46	2.309 (0.7646)	45	0.920 (0.7775)	0.209
FSH (IU/L) (a)	M: 1-15 F: 2-138					
Baseline		49	4.70 (0.383)	50	4.74 (0.379)	0.943
Change from Baseline at Week 4		46	0.22 (0.358)	45	0.62 (0.367)	0.434
LH (IU/L) (a)	M: 2-12 F: 0-105					
Baseline		49	6.73 (1.160)	50	5.21 (1.149)	0.354
Change from Baseline at Week 4		46	0.23 (0.936)	45	1.31 (0.957)	0.423

Sources. Tables 14.2.0, 14.2.3.2, 14.2.4.2, 14.2.5.2, 14.2.6.2, 14.2.9.2 and 14.2.10.2 and Appendices 16.1.9.2.12, 16.1.9.2.14, 16.1.9.2.16, 16.1.9.2.18, 16.1.9.2.27 and 16.1.9.2.30.
All means are expressed as LS means
(a) Normal ranges for estradiol, LH and FSH for women were defined as the lowest value among the menstrual phases to the highest value among the menstrual phases.

There were 2 patients in the placebo group and 4 in the ramelteon group that had total testosterone levels below the lower limits of normal at Week 4 and at the End of the Double-Blind period (source Table 14.2.3.4). No patients in either treatment groups had *free* testosterone levels below the normal range during any period of evaluation (source Table 14.2.4.3).

Significant differences in baseline estradiol levels were noted between treatment groups; however, the applicant stated that these values were not collected with regard to menstrual cycles. No patients had estradiol levels that were outside the normal range at any period of evaluation (source Table 14.2.5.3).

Three patients in the placebo group and 2 patients in the ramelteon group had a shift from normal to high prolactin level at Week 4 (source Table 14.2.6.4). Considering labs from all study visits, there was a higher incidence of *blood prolactin increased* reported as an adverse event in the placebo group (10.2%) than the ramelteon group (6.0%). Prolactin levels were only mildly elevated based on review of the dataset (DLAB1.xpt for Study TL-375-01). For the ramelteon group, the range of elevated prolactin levels was from 19.2 (one male) to 29.05 (female). These are only slightly above the normal reference range (males 1.61-18.77; females 1.39 – 24.2).

Adrenal Axis (source Tables 14.2.7.3 and 14.2.8.3)
There were no statistically significant differences in the mean changes from baseline to Week 4 for ACTH and morning cortisol levels between treatment groups. One patient in the placebo group had a follow-up cortisol level that was below the lower limits of normal. No patients in either treatment group had an ACTH below the lower limits of normal at Week 4 of at the end of the Double-Blind period. ACTH stimulation testing was not performed as part of the safety evaluation in this study.

Conclusions on TL-375-031 Endocrine Safety Results
There were no significant differences in the mean changes from baseline to Week 4 for the endocrine parameters evaluated in TL-375-031. Review of datasets to evaluate individual data reported as out of normal range did not provide evidence of clinically significant changes in these endocrine parameters for any single patient. The short duration of this study (4 weeks) precludes any definitive conclusion regarding the effects of ramelteon on endocrine function, particularly the reproductive axis.

TL-375-032
This was a 6-month, randomized, double-blind, placebo-controlled, parallel group study in healthy men and women with chronic insomnia. After a 21-day screening period, eligible subjects were randomly assigned (1:1) to receive either ramelteon 16 mg or placebo once daily for a total of 6 months. This was followed by a 2-week Washout Period. The primary objective of this study was to determine if long-term (6 months) administration of ramelteon 16 mg daily had an effect on endocrine function in patients with chronic insomnia.

The patient population was comprised of healthy men and premenopausal women aged 18 to 45 years, inclusive, who had chronic insomnia. Eligibility criteria relevant to this consult included:

- no use of hormonal contraceptive
- had normal prolactin, LH, FSH, ACTH, TSH, T3 and T4 levels at baseline
- men had serum testosterone levels ≥ 150 ng/dL
- women had serum estradiol values within normal range
- no current significant endocrine or metabolic disease unless currently controlled and stable with protocol-allowed medication 30 days prior to Day 1
- excluded medications included the following: systemic steroids, OTC or Rx meds that may interfere with study evaluation, all hormonal medications (see Final Study Protocol, section 6.4)

Endocrine tests at baseline included ACTH stimulation, prolactin, ACTH, cortisol, T3, T4 (free and total), TSH, LH, FSH, free and total testosterone (males only), and estradiol (females only). A menstrual history was obtained during the screening evaluation for women.

During the study, the following endocrine tests were obtained monthly: prolactin, ACTH, cortisol, T3, T4 (free and total), TSH, LH, FSH, free and total testosterone and estradiol . In addition, women were provided with an LH surge home test kit and a menstrual diary. The ACTH stimulation test was repeated at Month 6.

The primary measure of safety was the change from Baseline in total T4. A repeated measures analysis of this variable over the 6 months of double-blind treatment in the ITT population was the primary analysis.

A total of 122 patients were randomly assigned to receive either placebo (n=65) or ramelteon 16 mg qd (n=57). The ITT population included all subjects who were randomized and received at least one dose of study medication. All 122 patients were included in the ITT analyses. The percentages of patients completing the study in both treatment groups was low (placebo 63%; ramelteon 44%). The most common reasons for study withdrawal included withdrawal of informed consent and adverse events.

The following table summarized certain baseline characteristics of this patient population.

Table 3.

Characteristic	Placebo n=65	Ramelteon 16 mg n=57	Overall N=122
Gender, n(%)			
Men	30 (46.2)	23 (40.4)	53 (43.4)
Women	35 (53.8)	34 (59.6)	69 (56.6)
Mean age in yrs (SD)	34.1 (7.30)	34.5 (8.07)	34.3 (7.64)

Protocol deviations were reported in 92.6% of the ITT population. Two of the secondary efficacy parameters, ACTH stimulation testing and LH surge tests, were among the reasons cited as protocol deviation.

Thyroid Hormone Tests

There was no overall statistically significant difference in the mean change from Baseline in total T4 between the 2 treatment groups (p=0.579). Evaluation of shifts in total T4 levels from Baseline to Months 1 through 6 and Follow-up (source Table 14.2.1.6) revealed only 2 instances when there was a shift from normal to high. This occurred in two patients in the placebo group at Month 1 testing. No patients in the ramelteon treatment group had a shift in total T4 levels outside of the normal range during the 6 months of treatment.

There were no overall statistically significant differences in the mean change from Baseline in Free T4, TSH, and T3 between the 2 treatment groups. The following table from the applicant's final study report summarizes these data.

Table 11.c Mean Values at Baseline and Mean Changes from Baseline for Thyroid Axis Variables

Variable (reference range) (a)	Placebo Group No. Subjects	Placebo Group LS Mean (SE)	Ramelteon 16 mg Group No. Subjects	Ramelteon 16 mg Group LS Mean (SE)	P- value (b)
Free T4 (0.8-2.4) pmol/L					
Baseline	65	13.2 (0.22)	56	12.5 (0.24)	0.058
Change from Baseline					
Month 1	54	-0.1 (0.18)	46	-0.2 (0.20)	0.792
Month 2	51	-0.2 (0.22)	42	0.0 (0.24)	0.489
Month 3	46	0.2 (0.20)	37	0.1 (0.22)	0.529
Month 4	41	-0.4 (0.25)	30	-0.4 (0.28)	0.932
Month 5	43	-0.3 (0.20)	26	-0.2 (0.26)	0.972
Month 6	42	0.3 (0.27)	24	0.1 (0.35)	0.636
Follow-up	45	-0.2 (0.22)	33	0.1 (0.26)	0.477
Overall (c)	---	-0.1 (0.13)	---	-0.1 (0.15)	0.969
					0.863 (d)
TSH (0.35-5.10) mIU/L					
Baseline	65	1.7 (0.13)	56	1.4 (0.14)	0.018
Change from Baseline					
Month 1	54	0.2 (0.08)	46	0.2 (0.09)	0.826
Month 2	51	0.1 (0.09)	42	0.2 (0.10)	0.423
Month 3	46	0.2 (0.12)	37	0.2 (0.13)	0.974
Month 4	41	0.3 (0.13)	30	0.2 (0.12)	0.429
Month 5	43	0.2 (0.09)	26	0.0 (0.10)	0.305
Month 6	42	0.1 (0.09)	24	-0.1 (0.12)	0.084
Follow-up	45	0.2 (0.11)	33	0.1 (0.12)	0.535
Overall (c)	---	0.2 (0.07)	---	0.1 (0.07)	0.426
					0.216 (d)
T3 (0.6-2.1) nmol/L					
Baseline	65	1.4 (0.03)	56	1.5 (0.03)	0.025
Change from Baseline					
Month 1	54	0.0 (0.03)	46	0.0 (0.04)	0.969
Month 2	51	0.0 (0.03)	42	0.0 (0.04)	0.854
Month 3	46	0.0 (0.03)	37	0.1 (0.04)	0.033
Month 4	41	0.0 (0.03)	30	0.0 (0.04)	0.385
Month 5	43	0.0 (0.03)	26	0.1 (0.04)	0.224
Month 6	42	0.0 (0.03)	24	0.0 (0.04)	0.967
Follow-up	45	0.0 (0.03)	33	0.0 (0.04)	0.827
Overall (c)	---	0.0 (0.02)	---	0.0 (0.02)	0.238
					0.081 (d)

Source: Tables 14.2.2.2, 14.2.11.2, and 14.2.12.2.
--- indicates not applicable
(a) Data for total T4 as shown in Table 11.a
(b) For comparison of placebo and ramelteon group means using Student's t-test
(c) LS means and P-values for the overall analysis are based on a repeated measures analysis of change from Baseline using an ANCOVA model
(d) For analysis of 6 nominal time-period interactions

A statistically significant difference in the effect of treatment over time on T3 was observed between the two treatment groups (p=0.011); however, there is no apparent clinical significance to this finding. Thyroid hormone levels (T4, free and total, or T3) should not be interpreted in isolation, but should be evaluated in conjunction with a TSH value. One patient had T3 levels outside of the normal range. Patient 321201 had elevated T3 levels of 2.13 on Day 1, 2.23 on Month 2 evaluation, and 2.31 at Month 6. All other visit values were normal and no abnormal TSH values were reported. T3 normal range was reported to be 0.69 to 2.1 nmol/L. The biochemical changes in this patient do not appear to be clinically relevant.

Two patients (3.5%) in the ramelteon group had abnormal TSH values reported (source Table 16.2.6.2). Patient 321305 had decreased TSH values at Month 6 and follow-up (0.22 and <0.06, respectively). T4 and T3 levels remained within normal ranges. Patient 321013 had an elevated TSH at Month 6 (5.27) with normal T4 and T3 levels. Five patients (7.7%) in the placebo group had abnormal TSH values reported.

In summary, there were no overall significant changes in thyroid function tests. Review of individual subject data with thyroid tests outside the normal range did not reveal any clinically significant changes or consistent abnormal laboratory changes.

Reproductive Axis

There were no overall statistically significant differences in the mean changes from Baseline for testosterone (total and free), estradiol, FSH, or LH between treatment groups. The percentage of patients having a low total testosterone in the placebo group was 20% (13/65) compared 19.3% (11/57) in the ramelteon group. There was a statistically significant difference in the mean change from Baseline in free testosterone between the two treatment groups at Month 1 (p=0.028); however, this represented a clinically insignificant mean increase from Baseline in the ramelteon group of 21.6 pg/mL. For total and free testosterone, the overall mean changes included slight increases in the ramelteon group compared to placebo. In contradistinction, the long-term, open-label study (discussed below Study TL-375-022) shows a decrease in testosterone levels. However, this was observed in older male subjects who were specifically enrolled and separately evaluated at the 8 mg dose.

There was an overall statistically significant difference in the mean change from Baseline for prolactin between the two treatment groups. The ramelteon group had a mean increase of 2.9 ug/L compared to a reduction of –0.6 ug/L in the placebo group (p=0.003). The applicant notes that significant differences in the mean change from Baseline for prolactin were observed only at the Month 1 and Month 4 timepoints. However, patients withdrawn from the study or who had study drug discontinued secondary to the elevated prolactin levels could account for lower prolactin values at subsequent lab visits. The following table summarizes the individual patients with elevated prolactin levels. (source Table 16.2.6.2)

Table 4.

Treatment/Patient	Gender/Age	Visit	Prolactin value	Normal at Baseline
Placebo				
321333	Female/39	Month 5	39.34	Y
321204	Male/33	Month 1	22.59	Y
321306	Female/27	Month 3 and follow-up	47.69, 28.98	Y
321358	Female/44	Day 1, Month 1, Month 3, Month 6, F/U	32.81, 26.89, 25.36, 27.06, 27.66	N
321117	Female/40	Day 1	35.04	N
321014	Male/25	Month 4	23.87	Y
321023	Male/24	Month 3	21.45	Y
321061	Male/22	Month 6	19.51	Y
321063	Male/25	Day 1	19.82	N
321206	Male/34	Month 2	20.53	Y
321309	Female/34	Screening, Day 1, Month 2, Month 3, Month 4	29.99, 31.09, 28.83, 28.68, 27.27	N
321069	Male/30	Month 2, Month 4, F/U	21.71, 20.55, 19.60	Y
321056	Male/24	Day 1, Month 4, Month 5	38.92, 20.76, 20.09	N
321148	Female/39	Screening, Day 1, Month 1, Month 3, Month 4, Month 5, Month 6, F/U	25.24, 29.70, 31.32, 35.37, 25.43, 28.46, 27.28, 29.68	N
321136	Female/18	Month 3	25.73	Y
321329	Female/28*	Screening, Day 1, Month 5, Month 6	24.73, 32.26, 26.19, 30.06	N
321339	Female/40	Month 4	24.92	Y
321209	Male/30	Month 1, Month 3, Month 4, Month 5, F/U	19.66, 19.87, 19.51, 25.54, 18.95	Y
321210	Male/31	Month 5	18.81	Y
321325	Female/31	Screening, Month 6, F/U	28.28, 26.60, 28.74	N
Ramelteon				
321336	Female/39	Month 1, Month 3, Month 4, Month 5	36.22, 34.78, 25.09, 26.91	Y
321343	Female/24	Month 2	53.60	Y
321344	Female/18	Month 3, Month 4	24.39, 32.88	Y
321369	Female/32	Month 1	32.53	Y
321094	Female/36	Month 1	69.95	Y
321095	Female/20	Month 4	30.38	Y
321026	Male/34	Month 6	19.32	Y
321119	Female/20	Screening	29.03	N
321120	Female/43	Screening	57.04	N
321010	Male/41	Month 2	19.40	Y
321022	Male/42	Follow-up	19.81	Y
321154	Female/27	Month 4	26.03	Y
321155	Female/44	Day 1, Month 1, Month 4	25.54, 28.56, 25.36	N
321140	Female/29	Follow-up	27.79	Y
321321	Female/33	Month 1	24.27	Y
321158	Female/40	Day 1	33.99, 28.28	N
321042	Male/28	Day 1, Month 1, Month 6, Follow-up	21.93, 43.29, 32.00, 34.43, 33.74	N
321135	Female/32	Month 2, Follow-up	39.90, 37.07	Y
321226	Male/41	Month 4	19.94	Y
321338	Female/32	Month 3	42.47	Y
321365	Female/20	Month 2	27.74	Y
321317	Female/43	Month 6	35.67	Y
321326	Female/43	Month 1, Month 3	25.21, 24.75	Y

normal range for males: 1.61-18.77 ug/L; normal range for females: 1.39-24.2 ug/L
*pregnant

There were 20 patients (30.1%) in the placebo group with elevated prolactin levels observed at some point in time during study evaluation, including screening and baseline. In comparison, there were 23 patients (40.3%) in the

ramelteon group with elevated prolactin levels during study evaluation. There was an equal number of males and females in the placebo group who had an elevated prolactin level reported. In contrast, there were 18 female patients treated with ramelteon who had an elevated prolactin level reported and only 5 males treated with ramelteon. The applicant evaluated mean prolactin values at baseline and mean changes from baseline by gender and noted that there was no overall statistically significant difference in the mean change from baseline between the two treatment groups **for men** (p=0.414); however, there remains a mean increase in the ramelteon group (1.2 ug/L) over placebo (0.2 ug/L) in men. **For women**, there was a statistically significant overall difference in mean change from Baseline in prolactin between the two treatment groups (p=0.003). The overall mean increase from Baseline in the ramelteon group was 4.9 ug/L for women and there was a mean decrease of –0.6 ug/L in the placebo group.

A total of 12 out of 65 placebo-treated patients had normal baseline prolactin levels which subsequently increased while on study drug (18.5%) while 18 out of 57 of the ramelteon-treated patients had an increase from normal baseline while on study drug (31.5%).

Prolactin is produced by lactotroph cells in the anterior pituitary gland. Its secretion and release are mediated by dopamine, and any process that disrupts dopamine secretion or interferes with the delivery of dopamine to the portal vessels may cause hyperprolactinemia. Medications which inhibit lactotroph dopamine receptors (e.g., metoclopromide, phenothiazines, butyrophenones), interrupt the delivery of dopamine to the portal vessels supplying the pituitary (e.g., risperidone, MAO inhibitors, TCAs), or directly stimulate pituitary lactotrophs (e.g., estrogens/oral contraceptives) can cause hyperprolactinemia. Other medications, through unknown mechanisms have also been reported to raise prolactin levels. In general, medication-induced hyperprolactinemia is associated with levels of prolactin in the range of 25 to 100 ug/L.[1] During pregnancy, prolactin levels increase approximately 10-fold. Levels may also rise after exercise, meals, stimulation of the chest wall, physical and psychological stress, but levels under these circumstances rarely exceed 40 ug/L.[1] After medications and normal physiologic processes have been excluded, pituitary (functioning and non-functioning adenomas) or hypothalamic diseases (tumors, infiltrative diseases) should be considered in the differential diagnosis of hyperprolactinemia. Primary hypothyroidism can also cause elevated prolactin levels via TRH stimulation of the lactotrophs.

The majority of patients in both treatment groups had increases in prolactin levels that were mild (20 to 30 ug/L) and normalized on subsequent lab draw while remaining on treatment. From source Table 16.2.6.2 there were 6 patients with prolactin levels > 40 ug/L; one patient received placebo and 5 patients received ramelteon. The placebo patient (321306) was a 27-yr old female who had normal screening and baseline prolactin levels. Her Month 3 level was elevated at 47.69 ug/L but subsequent lab draws were normal. A follow-up lab test off study treatment revealed an elevated prolactin of 28.98 ug/L. No additional information is available. Two patients in the ramelteon group with prolactin levels > 40 ug/L had baseline elevations of prolactin levels at screening (321120) or baseline (321042). Patient 321120 had a prolactin at screening (Day –19) of 57.04 ug/L. Repeat screening showed normal prolactin level and all other values at all subsequent visits were normal. Patient 321042 was terminated from study and referred to an endocrinologist for persistently elevated prolactin levels. Screening prolactin level was 21.93 ug/L which remained above normal after study drug was initiated and at follow-up off drug treatment. The remaining three patients in the ramelteon group had elevated prolactin values > 40 ug/L observed after the initiation of study medication and had normalization of prolactin values after study discontinuation. Subject narratives are summarized below:

Patient 10366/321343 was a 24-yr old female who was randomized to ramelteon 16 mg with normal screening and baseline prolactin levels. Her Month 2 prolactin level was elevated at 53.6 ug/L and she was discontinued from the study. Repeat prolactin levels at Month 6 and follow-up showed normalization of prolactin levels (9.11 and 11.96 ug/L, respectively).

Patient 12925/321094 was a 36-yr old female who was randomized to ramelteon 16 mg with normal screening and baseline prolactin levels. Her Month 1 prolactin level was elevated at 69.95 ug/L and she was discontinued from the study. Repeat prolactin level 10 days later showed a normalization of prolactin level to 19.07 ug/L.

Patient 20876/321338 was a 32-yr old female who was randomized to ramelteon 16 mg with normal screening and baseline prolactin levels. Her Month 3 prolactin level was elevated at 42.47 ug/L. She was discontinued from the

[1] Schlechte, JA. Prolactinoma. *N Eng J Med* 2003;349:2035-2041.

study with 'withdrawal of consent' listed as the reason for study termination: Her prolactin levels at Month 6 and follow-up visits were normal (22.61 and 23.33, respectively).

Chronic hyperprolactinemia can result in gonadal dysfunction as a result of increased prolactin levels having an inhibitory effect on the hypothalamic pulsatile release of gonadotropin-releasing hormone (GnRH) and inhibiting the positive feedback effect of estradiol levels on luteinizing hormone. In addition to infertility, hypogonadism can result in osteopenia and osteoporosis. Bone density is normal in women with hyperprolactinemia who continue to have regular menses.[2,3] The incidence of amenorrhea in this trial was 6.2% in the placebo group compared to 1.8% in the ramelteon group. None of the three ramelteon-treated patients with prolactin levels > 40 ug/L had amenorrhea reported as an adverse event.

The summary of menstrual diaries revealed little difference between the two treatment groups; however, 25.9% of the ramelteon-treated subjects stated that they did not have normal menses compared to 13.8% in the placebo-treated group. Review of the menstrual diary records listed only one ramelteon-treated subject reporting no menses for Months 4 and 5. This subject (321133) had no increases in prolactin levels, was not reported to be hypothyroid, or have any abnormalities of reproductive endocrine hormone tests. There were two pregnancies reported in the placebo group.

The applicant reported no notable differences between the treatment groups for the LH surge tests; however, many subjects failed to perform these tests on appropriate days or did not perform them at all as noted under the listing of protocol deviations.

Adrenal Axis

There were no overall statistically significant differences in the mean change from Baseline for ACTH and morning cortisol levels between the two treatment groups. No clinically meaningful differences in shifts of lab values from low/nl to high or high/nl to low were observed between the treatment groups for ACTH or morning cortisol levels. Given the pulsatile secretory pattern of both ACTH and cortisol, evaluation of the adrenal axis via this approach is limited unless extreme deviations from the normal ranges are observed.

This study also tested the adrenal function through ACTH stimulation at baseline (Day 1) and at Month 6. Protocol deviations in which no ACTH stimulation testing was performed or serum cortisol was not obtained at specified collection time (0, 30min, 60min) were present in both treatment groups. No positive ACTH stimulation tests were observed in patients with valid test results.

Conclusions on TL-375-032 Endocrine Safety Results

This was a 6-month, placebo-controlled study evaluating the safety of ramelteon 16 mg qd on the endocrine system including the thyroid axis, reproductive axis, and the adrenal axis. There were no clinically significant differences between ramelteon and placebo for thyroid and adrenal axis parameters. There was a statistically significant difference in the overall mean change in prolactin levels from Baseline to End of Treatment with an overall mean increase in the ramelteon treatment group of 2.9 ug/L compared to a –0.6 ug/L change in the placebo group. A higher percentage of patients in the ramelteon group had an increase in prolactin levels from normal at baseline (31.5%) than placebo (18.5%). While the majority of patients in both groups had mildly increased prolactin levels in the 20 to 30 ug/L range which normalized with continued treatment, there were slightly more patients in the ramelteon group (n=5) compared to placebo (n=1) who had increases greater than 40 ug/L. Three of the ramelteon patients had increases after initiation of therapy which normalized with discontinuation of drug. While the three cases are not conclusive evidence of drug causality, data from published literature have noted an association between melatonin levels and prolactin elevations.[4] In addition, melatonin levels were increased in mice receiving TAK-375 at 30 mg/kg/day and rats receiving doses of 60 mg/kg/day.[5]

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[2] Klibanski A et al. Decreased bone density in hyperprolactinemic women. *N Engl J Med.* 1980;303:1511-1514.
[3] Klibanski A et al. Effects of prolactin and estrogen deficiency in amenorrheic bone loss. *J Clin Endocrinol Metab.* 1988;67:124-130.
[4] Karasek M et al. Melatonin circadian rhythm in women with idiopathic hyperprolactinemia. *Neuro Endocrino Lett.* 2004; 25(6):411-415.
[5] Data from M-11-709 and M-11-599

The consequences of chronic hyperprolactinemia include gonadal dysfunction (e.g., amenorrhea, infertility) and decreased bone mineral density as a result of decreased testosterone or estradiol levels. While much of our understanding of the clinical effects of hyperprolactinemia comes from studies in patients with prolactin-secreting tumors, several investigators have described the effects of prolactin elevation secondary to antipsychotic drugs on reproductive function, sexual function, and bone density.[6,7,8] The results from TL-375-032 showed a statistically significant greater increase in prolactin levels associated with ramelteon use compared to placebo. This study did not demonstrate any clinical significance resulting from this finding; however, there were only a few patients with markedly elevated prolactin levels (i.e., > 40 ug/L) and duration of treatment was limited to only 6 months. Further evaluation of ramelteon's effects on prolactin levels and the long-term consequences on reproductive function should be considered.

TL-375-022

This was an open-label, uncontrolled, fixed-dose study of ramelteon 16 mg daily in patients, age 18 to 64 years, and ramelteon 8 mg daily in patients, age 65 years or older. Patients naïve to ramelteon or who have participated in prior ramelteon studies were eligible for this study. Subjects who had previously participated in an allowed ramelteon study, and who had completed all final visit procedures for the previous study within 21 days of the Treatment Initiation Visit for this study, were not required to have all Screening procedures repeated. The primary objective of this study was to assess the long-term safety of regular use of ramelteon. Analyses were performed on the ITT population which was subdivided further into the following:

- 24-week compliant – these were subjects who had taken an average of 3 doses or more of ramelteon per week during the first 24-week period of the study
- 48-week compliant – these were subjects who had taken an average of 3 doses or more of ramelteon per week during the first 48-week period of the study

The key differences between TL-375-022 and the earlier studies (TL-375-031 and TL-375-032) are the longer duration of study *and* the inclusion of older patients, including postmenopausal women.

Endocrine safety assessments included:

- TSH, total and free T4, T3, and FTI - obtained at Baseline lead-in, Months 2, 4, 8, and Final Visit
- morning cortisol - obtained at Baseline, Months 1, 2, 4, 8, and Final Visit
- total and free testosterone (males only) - obtained at Baseline, Months 1, 2, 4, 8, and Final Visit
- LH and FSH (males only) - obtained at Baseline, Month 4, and Final Visit
- menstrual diary (premenopausal females only) - monthly

A total of 1,213 patients enrolled in the study. As of 20 September 2004 (data interim lock date), 337 subjects were ongoing in the study. The following table summarizes the disposition of subjects.

[6] Misra M et al. Effects of psychiatric disorders and psychotropic medications on prolactin and bone metabolism. *J Clin Psychiatry*. 2004;65(12):1607-1618.
[7] Smith S. Effects of antipsychotics on sexual and endocrine function in women: implications for clinical practice. *J Clin Psychopharmacol*. 2003:23(3Suppl1):S27-32.
[8] Naidoo U et al. Hyperprolactinemia and bone mineral density: the potential impact of antipsychotic agents. *Psychoneuroendocrinology*. 2003;28(Suppl2):97-108.

Category	Treatment: Ramelteon 8 mg N=248 n (%)	Treatment: Ramelteon 16 mg N=965 n (%)	Total N=1213 n (%)
Completed Open-Label Treatment Period	45 (18.1)	122 (12.6)	167 (13.8)
Ongoing	61 (24.6)	276 (28.6)	337 (27.8)
Discontinued from Open-Label Treatment	142 (57.3)	567 (58.8)	709 (58.5)
Adverse event(s)	29 (11.7)	116 (12.0)	145 (12.0)
Lack of efficacy	61 (24.6)	176 (18.2)	237 (19.5)
Protocol deviation	11 (4.4)	44 (4.6)	55 (4.5)
Withdrawal of consent	25 (10.1)	107 (11.1)	132 (10.9)
Lost to follow-up	1 (0.4)	84 (8.7)	85 (7.0)
Death	0 (0.0)	2 (0.2)	2 (0.2)
Investigator discretion	5 (2.0)	7 (0.7)	12 (1.0)
Pregnancy	0 (0.0)	3 (0.3)	3 (0.2)
Other	10 (4.0)	28 (2.9)	38 (3.1)
Completed Single-Blind Placebo Run-out Period	45 (18.1)	118 (12.2)	163 (13.4)
Discontinued from Single-Blind Placebo Run-out	0 (0.0)	4 (0.4)	4 (0.3)
Protocol deviation	0 (0.0)	2 (0.2)	2 (0.2)
Lost to follow-up	0 (0.0)	2 (0.2)	2 (0.2)

Source: Table 14.1.2.1.
Includes all data up to the interim lock date of 20 September 2004.

Of the 1,213 subjects, 596 were included in the 24-week compliant subgroup analysis and 168 were included in the 48-week compliant subgroup analysis.

The gender and age of the ITT population are summarized in the following table.

Table 5.

Characteristic	Ramelteon 8 mg n=248	Ramelteon 16 mg n=965	Total N=1213
Gender, n(%)			
male	116 (46.8)	385 (39.9)	501 (41.3)
female	132 (53.2)	580 (60.1)	712 (58.7)
mean age in yrs (SD)	72.3 (5.58)	46.2 (11.87)	51.6 (15.15)

47.6% of the women in the ramelteon 8 mg group were postmenopausal compared to 21.0% in the ramelteon 16 mg group. Thyroid hormone therapy was listed as a concomitant medication used in 14.9% of the ramelteon 8 mg group and 5.7% of the 16 mg group.

Although the intent of TL-375-022 was to obtain long-term safety data on ramelteon, the majority of patients in the ITT population had study medication exposures of < 32 weeks of study medication as a result of high discontinuation rates (58.5% discontinued overall). Only 77 patients (17 in the 8 mg dose group and 60 in the 16 mg dose group) had drug exposure beyond 48 weeks (source Table 14.1.11.1).

Thyroid Axis

The following table summarizes the incidence of out of normal range values for thyroid laboratory tests in the ITT population who had normal baseline values for the particular test

Table 6.

Laboratory Parameter	Normal range	Ramelteon 8 mg n=248	Ramelteon 16 mg n=965
FTI	1.1-4.6	2 (0.8)	0
TSH (mU/L)	0.32-5	21 (8.5)	31 (3.2)
T3 (nmol/L)	0.69-2.11	6 (2.4)	19 (2.0)
T4 (nmol/L)	54-161	6 (2.4)	8 (0.8)
free T4 (pmol/L)	9-24	2 (0.8)	3 (0.3)

Review of listing of subjects (source Table 14.3.4.5) with at least one abnormal TSH value, regardless of baseline status, identified 73 out of 1,213 (~6%) patients in this cohort. Thirty-five of these had low TSH values, 36 had elevated TSH values, and two had both low and high TSH values reported on separate occasions.

A low TSH value often indicates increased thyroid hormone activity or hyperthyroidism. The majority of patients with a reported low TSH value had values that were slightly below the lower limit of normal (0.32 mU/L), and many of these subjects normalized on subsequent visits. There were nine patients with TSH values < 0.06, highly suggestive of excessive thyroid hormone activity. Four occurred in the 8 mg dose group and 5 were in the 16 mg dose group. All but one of the nine subjects had abnormal TSH values at Baseline; however, the listings did not identify which patients were naïve to therapy and which patients continued from a previous clinical study. The one patient who had a normal TSH value at lead-in time-point had a suppressed TSH value at the final visit and no additional information was provided. One other patient (10734/222036) was on exogenous LT4 for treatment of thyroid cancer. It is likely that this patient's suppressed TSH is secondary to her thyroid cancer treatment (i.e., LT4 suppression of TSH).

An elevated TSH value may indicate inadequate thyroid hormone activity. A patient is considered hypothyroid if the elevated TSH is accompanied by a low free T4 level. Patients with an elevated TSH level and a *normal* free T4 level are often considered to have subclinical hypothyroidism. Three patients (12716/251073, 12766/201328, 12704/201142) had both elevated TSH levels and decreased free T4 values. One patient was on the 8 mg dose and two were on the 16 mg dose.

The majority of patients with at least one reported TSH elevation had values that were only slightly increased (e.g., > 5.0 to 8.0 mU/L) without an accompanying decreased free T4 level. Five patients had a TSH value > 10 mU/L. While none of these patients had accompanying decreased free T4 levels, other TSH values remained above normal, and in one patient (12666/211388) there was persistent TSH increase above 10 mU/L at 5 different time-points including a peak TSH value of 35.65 mU/L. Free T4 levels for this patient was low normal between 10 to 14 pmol/L.

In summary, 73 patients (6%) had abnormal TSH values in Study TL-375-022. Only a few of these patients had *both* abnormal TSH values and free T4 levels to meet a diagnosis of primary thyroid disorder. Several patients had a mildly elevated TSH value that likely represent subclinical hypothyroidism. The absence of a control group is a major limitation in making any conclusion on these thyroid laboratory abnormalities. However, the incidence of abnormal TSH values in this study (6%) is similar to the placebo rate observed in the 4-week (6.1%) and 6-month studies (7.7%). Thyroid disorders are common in the general population and the laboratory abnormalities in this long-term, open-label study likely reflect the background rate of thyroid dysfunction.

Reproductive Axis

The following table summarizes the incidence of out of normal values for laboratory tests of male reproductive function in patients who had normal Baseline values.

Table 7.

Laboratory Parameter	Normal range	Ramelteon 8 mg n=248	Ramelteon 16 mg n=965
Total testosterone (ng/dL)	350-1030	17 (6.9)	69 (7.2)
free testosterone (pg/mL)	52-280	33 (13.3)	57 (5.9)
LH (IU/L)	1-15	3 (1.2)	5 (0.5)
FSH (IU/L)	1-12	6 (2.4)	12 (1.2)

The overall abnormality noted with the evaluation of the reproductive axis was decrease in mean total and free testosterone levels in the 8 mg dose group. The decrease in mean total testosterone was in the range of 5.9 to 8.7% from Baseline to Months 4 and 8 and 7.4 to 16.5% for mean free testosterone from Baseline to Months 2, 4, and 8. For the 16 mg dose group, there were slight increases in mean testosterone levels over time.

Testosterone is secreted in a pulsatile fashion and the evaluation of hypogonadism should therefore include at least three early morning serum total testosterone measurements. Free testosterone measurements should be considered if one suspects sex hormone-binding globulins to be low. Unequivocally low testosterone levels should be further evaluated with a serum LH level to determine if the hypogonadism is primary or secondary.

Review of the individuals with testosterone levels below the lower limit of normal showed a majority with abnormal levels at the lead-in/Baseline period. In addition, the majority of patients had levels that were reported low but remained in the 250 to < 350 pg/dL range. In this trial, investigators identified 20 subjects with total testosterone below the normal reference range that were considered to be clinically significant. Among these subjects, 13 also had low free testosterone levels. Eight of these subjects had LH measurements performed at the same time-point and all were normal except one subject who had LH values below and above the normal reference range. None of these subjects had an adverse event related to sexual dysfunction.

While there was a substantial number of individuals with testosterone levels outside the normal reference range in this study, the absence of a placebo group limits any conclusions that can be drawn from such results. A comparison between the 8 mg and 16 mg dose groups is inappropriate as these two groups represented an older and younger population, respectively. Many studies have documented a reduction in serum testosterone levels in men as they age. Overall, no conclusions can be made regarding changes in testosterone level in this study; however, the 6-month placebo controlled study showed similar incidence of low testosterone levels between placebo and ramelteon treatment groups (20% vs 19.3%).

Prolactin levels were not routinely measured in this long-term, open-label study. The absence of these data is relevant as the 6-month, placebo-controlled study showed a significant increase in mean prolactin levels with ramelteon 16 mg from baseline relative to placebo. Review of the AE dataset for Study -022 did not reveal any reports of amenorrhea or galactorrhea. There were 5 patients (2 female and 3 males) who reported either decreased libido or decreased sex drive but none of these patients had reported elevated prolactin levels.

There was one patient (subject 12817/221265) who was diagnosed with a prolactinoma while enrolled in Study TL-375-022. This was a 29 year old female who was G0P0. She began treatment with ramelteon 16 mg on 7 August 2003. Beta HCG was negative prior to study drug treatment. Medications used included ortho tri-cylcin (July 2002 through 15 Sept 2003), MVI, and ibuprofen. In [ ] the patient noted cessation of menses, headaches, and mild hair loss. Laboratory studies on [ ] were all within normal limits with exception for DHEA 982 (nl 130-980 ng/dL) and prolactin 114.4 (nl 2.8-29.2 ng/mL). Her medication was stopped on 22 March 2004 on study day 228. A beta HCG test was negative on [ ] An MRI of the pituitary revealed an asymmetric pituitary gland; the right side was slightly larger than the left and contained an ovoid focus [ ] cm) of diminished signal that did not enhance with contrast. No other notable findings. The lesion was consistent with a pituitary microadenoma. Examination revealed hirsutisim of chin, neck, and lower abdomen and bilateral galactorrhea. Pelvic examination was normal. She was started on bromocriptine on 12 April 2004 at a dose of 1.25 mg daily. This dose was subsequently doubled. Menstrual cycles resumed and she was seen at a follow-up visit on 20 May 2004. Prolactin level on 12 May 2004 was 106.6 ng/mL and on 9 July 2004 had decreased to 27.7 ng/dL. The investigator considered this event to be possibly related to study drug.

Patient 221265 had a typical presentation for a prolactin-secreting tumor. In women, amenorrhea is often observed after the discontinuation of oral contraceptives, but there is no apparent relation between the use of OCPs and formation of prolactinomas. The patient reported cessation of menses in [redacted] but prolactin levels were not measured until March 2004, approximately 7 months after starting drug therapy. An evaluation in September may have yielded useful information as the patient would have only been on therapy for one month and if a prolactinoma was diagnosed at that point, it would have been unlikely related to ramelteon therapy. Regardless, this presentation is not evidence that the prolactinoma was due to ramelteon therapy. Pituitary adenomas are not uncommon and have been reported to be found in 10 to 25% of unselected autopsy series. Of these, prolactinomas are the most common type of functional pituitary tumor, comprising approximately 40% of all pituitary adenomas. While study TL-375-032 revealed increases in prolactin levels associated with ramelteon therapy, this one case of prolactinoma out of 1,213 patients treated in TL-375-022 is insufficient evidence to conclude that ramelteon induces adenomatous growth of the pituitary lactotrophs.

Adrenal Axis

There were 22 patients (6 in the 8 mg dose group and 14 in the 16 mg dose group) who had out-of-normal range cortisol levels that were considered clinically significant by the investigator. All but one subject had normal values at Baseline. The majority of these patients had low morning cortisol levels (n=19) and 3 had elevated levels. Only one of these patients had more than two clinically significant out-of-range values. All others were limited to a single value. Review of the individual data listings for morning cortisols revealed that elevations or decreases tended to be mild and resolved on the next visit.

ACTH stimulation tests were performed on 10 patients who had a low morning cortisol reported. The following table summarizes the results in these 10 patients. Two patients had abnormal ACTH stimulation tests. Subject 10904/222070 was a 68-year old male (8 mg group) who had normal Baseline and Month 1 morning cortisol levels. His Month 2 cortisol level was low at 55 nmol/L. An ACTH stimulation test on Day 68 was abnormal and the patient was discontinued from the study on Day 92. Morning cortisol on Day 92 was normal but not follow-up ACTH stimulation test was performed. Subject 10823/201726 was a 56-year old male (16 mg group) who had normal morning cortisol levels at Baseline and Month 1. His Month 2 level was low at 83 nmol/L but was normal upon repeat testing on three occasions. His levels decreased again at Month 8 to < 28 nmol/L at which time he was withdrawn from the study and underwent ACTH stimulation testing which was abnormal. No additional information was available.

Subject Number/ Treatment Group	Gender/ Age (a)	Baseline AM Cortisol Value (b) (nmol/L)	Prompting AM Cortisol Value (b) (nmol/L)/ Study Day (c)	ACTH Stimulation Test Values (nmol/L)/ Time-point	Normal Results (d) (Y/N)	Discontinued Due to Cortisol Result? (Y/N)
10904/222070/ ramelteon 8 mg	Male/ 68	166	55/Day 57	83/0 mins 221/30 mins 276/60 mins	N	N
12552/170143/ ramelteon 8 mg	Male/ 67	359	110/Day 106	248/0 mins 580/30 mins 635/60 mins	Y	N
12724/251244/ ramelteon 8 mg	Male/ 73	166	110 (e)/Day 35	138/0 mins 497/30 mins 607/60 mins	Y	N
10430/221054/ ramelteon 16 mg	Female/ 37	248	138/Day 65	442/0 mins 414/30 mins 497/60 mins	Y	N
10823/201726/ ramelteon 16 mg	Male/ 56	276	<28 (e)/Day 240	<28/0 mins 193/30 mins 248/60 mins	N	Y
12635/201897/ ramelteon 16 mg	Female/ 45	248	138 (e)/Day 126	193/0 mins 524/30 mins 607/60 mins	Y	N
12643/221004/ ramelteon 16 mg	Female/ 32	248	- (f) -	193/0 mins 580/30 mins 690/60 mins	Y	N
12679/221183/ ramelteon 16 mg	Female/ 28	304	110/Day 56	166/0 mins 607/30 mins 690/60 mins	Y	N
12694/201015/ ramelteon 16 mg	Female/ 44	110	110 (e)/Day -15	166/0 mins 718/30 mins 828/60 mins	Y	N
12714/221441/ ramelteon 16 mg	Female/ 55	193	138/Day 57	248/0 mins 773/30 mins 856/60 mins	Y	N

Source: Table 14.3.4.1, Appendices 16.2.2, 16.2.7.2, and 16.2.8.2.
Includes all data up to the interim lock date of 20 September 2004.
(a) Age calculated as difference in whole years of screening date and date of birth.
(b) Normal ranges: Male 18-150 = 138-442 nmol/L; Female 18-150 = 166-718 nmol/L.
(c) Relative to day of first dose of open label medication.
(d) Normal results were defined as cortisol >18 µg/dL (497 nmol/L) at 30 or 60 minutes.
(e) The last AM cortisol value that was less than the gender-specific lower limit of normal and on or prior to the date of the ACTH stimulation test was included in this table because Appendix 16.2.8.2 did not specify which AM cortisol value prompted an ACTH stimulation test.
(f) Although all AM cortisol results included for this subject in Appendix 16.2.8.2 were within normal limits, an ACTH stimulation test was performed.

In summary, there were two patients (0.16%) with abnormal morning cortisol levels who subsequently had further evaluation with ACTH stimulation testing which were abnormal. No patients in the two controlled studies had abnormal ACTH stimulation tests or had significant differences between treatment groups for adrenal axis studies.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The thyroid, reproductive, and adrenal axes were evaluated in three clinical trials. Overall, there were no significant differences between placebo and ramelteon for many of the endocrine parameters measured in TL-375-032 and -035. The placebo rates observed in these two trials gave some reassurance that the rates observed in the uncontrolled, long-term study likely reflected the background risk in the general population and not an effect of drug therapy. Specifically, no consistent abnormalities in testosterone or thyroid levels were observed.

Ramelteon 16 mg administered daily for 6-months in a placebo-controlled study was associated with a significantly greater mean change in prolactin levels than placebo. In this trial, more patients treated with ramelteon had prolactin values > 40 ug/L than placebo. None of these patients had serious clinical consequences resulting from the prolactin elevation (e.g., amenorrhea, decreased libido). Review of published literature has shown an association between melatonin levels and increased prolactin levels. Furthermore, data from two non-clinical studies demonstrating an increase in melatonin levels associated with ramelteon administration suggest a plausible mechanism for prolactin elevation secondary to ramelteon administration.

While the degree of prolactin elevation in this one clinical study was not in the range observed with prolactinomas nor were there any serious adverse events observed as a result of the elevated prolactin levels, the duration of therapy and number of patients evaluated were inadequate to exclude the possibility that ramelteon can be associated with chronic hyperprolactinemia. Persistent hyperprolactinemia, even mild elevations secondary to drug therapy, may have an inhibitory effect on the hypothalamic pulsatile release of gonadotropin-releasing hormone (GnRH) and inhibit the feedback effect of estradiol on luteinizing hormone (LH). Dysregulation of the reproductive axis by persistent hyperprolactinemia may result in hypogonadism which may present as amenorrhea in women and infertility and decreased libido in both genders. Hypogonadism is also a risk factor for osteopenia/osteoporosis. Consequently, it is recommended that patients treated with ramelteon who present with amenorrhea or sexual dysfunction have a prolactin level checked as part of the clinical evaluation. Routine monitoring of prolactin levels while on ramelteon therapy is *not* recommended as prolactin elevation can also occur secondary to non-pathologic etiologies (e.g., stress). Therefore, monitoring is recommended based only on clinical complaints/presentation.

As stated previously, differences in prolactin levels were observed in only one placebo-controlled study which enrolled only 122 patients (randomized 1:1) for 6 months of therapy. Monitoring of prolactin levels in future studies in this clinical development program should be considered to obtain additional data on the extent and persistence of this laboratory abnormality.

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