CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-782

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to NDA 21-782 Clinical Pharmacology Biopharmaceutics Review

NDA: 21-782	Original Submission Date: 9/21/04
Submission Type; Code:	Original; 1S
Brand/Code Name:	[ ]
Generic Name:	Ramelteon (TAK-375)
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	Takeda Global Research & Development Center, Inc
Relevant IND(s):	58,136
Formulation; Strength(s):	Tablet; 8 mg
Proposed Indication:	Treatment of insomnia
Proposed Dosage Regimen:	8 mg QD

This addendum addresses the ramelteon's in vitro stability issues related to BCS Classification and proposes the final decision.

Takeda Global Research & Development Center, Inc has originally submitted NDA 21-782 on 9/21/04 for approval for the treatment of insomnia [ ]

No bioequivalence studies were conducted to compare clinical (Phases I and II/III) and to-be-marketed formulations. The Applicant claimed that ramelteon met BCS Classification 1 category. The Applicant's supporting data were presented in the Section 2.5 of the original NDA review (see Appendix 2 for recreation of Section 2.5).

During the reviewing cycle, the Applicant's data were forwarded to the BCS Committee, and the Committee has suggested studying ramelteon in vitro stability in simulated gastric and intestinal fluids. This recommendation was communicated to the Applicant.

On June 27, 2005 the Applicant submitted the requested in vitro stability of ramelteon in simulated gastric and intestinal fluids. The in vitro data appear to show that ramelteon is stable in both gastric and intestinal fluids (see Appendix 1). Therefore, the overall information submitted by the Applicant show that ramelteon met BCS Classification 1 category.

Appendix 1

Biopharm:

1. The Agency is in a final stage of evaluating ramelteon's BCS classification, and is seeking information on ramelteon stability in simulated gastric fluid (SGF; e.g., ramelteon exposure for 1 hour) and simulated intestinal fluid (SIF; e.g., ramelteon exposure for 3 hours). You are requested to generate and submit such data if not already available.

Response: Ramelteon reference standard was dissolved in both USP Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) to make a solution of approximately [ ] µg/mL. This concentration was chosen, as it is similar to the concentration of a [ ] release of an 8 mg tablet in 900 mL of fluid. The solutions were maintained at 37 °C during the study. Samples of each solution were taken at regular intervals and tested using the stability indicating HPLC method for assay in section 3.2.P.5.3 (report M-11-00530).

The results of the experiments are summarized in the tables below:

Stability of Ramelteon in Simulated Gastric Fluid at 37 °C

Time Point	*Concentration (µg/mL)*	*Percent of Initial*
Initial	*8.5*	
30 minutes	*8.5*	
60 minutes	*8.5*	

Stability of Ramelteon in Simulated Intestinal Fluid at 37 °C

Time Point	*Concentration (µg/mL)*	*Percent of Initial*
Initial	*8.5*	
30 minutes	*8.6*	%
60 minutes	*8.6*	%
120 minutes	*8.7*	%
180 minutes	*8.7*	%

All values were within +/-5% of the initial results over the time period tested, and therefore ramelteon can be considered stable in the GI tract according to the August 2000 BCS guidance document.

Appendix 2

Summary of the Applicant's BCS Classification Data

The solubility of the drug substance covers over the pH range 1.1 to 7.5 at 37°C using standard aqueous buffers described in USP 26. The permeability data of the drug substance was from the mass balance study (ADME of a single 16 mg dose of

[14C]ramelteon) in healthy adult male subjects and in vitro Caco-2 cell intestinal permeability study. Additionally, in vitro rat portal vein metabolism study was conducted to show the ramelteon gut absorption characteristics. To bridge the formulations throughout development and to support the waiver of in vivo bioequivalence studies, the dissolution of the ramelteon drug product was tested. The dissolution conditions used were USP Apparatus II at 50 rpm and 37°C, in 900 mL of each of 3 different media (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer).

Solubility

The solubility of the drug substance was established over the pH range 1.1 to 7.5 at 37°C using standard aqueous buffers. The ramelteon drug substance is a neutral compound, having no acid or base functional groups. The solubility of ramelteon was independent of pH under the conditions of this study, being [ ] mg/mL over the pH range 1.1 to 7.5 at 37°C. These data indicate that approximately [ ] mg of ramelteon would dissolve in a 250 mL aqueous solution at 37°C. This amount corresponds to approximately 8- to 10-fold more than the recommended therapeutic dose of ramelteon (8 mg).

Permeability

Mass balance study:

The mass balance study was conducted (a single 16 mg dose of [14C]ramelteon) in healthy adult male subjects. Urinary and fecal excretion of the administered radioactive drug was quantified. The mean radioactivity excreted in urine for the 6 subjects was 84%, indicating that at least 84% of the administered dose was absorbed through the gut. The mean radioactivity recovered in feces was 4.0% with less than 0.1% of that amount attributable to unchanged drug. These data suggest that the majority of the dose recovered in feces resulted from biliary excretion of absorbed drug as metabolites. The total percentage of ramelteon dose absorbed was approximately 88%.

In vitro permeability study:

The intestinal permeability of ramelteon was also investigated in an in vitro Caco-2 cell permeability assay using [14C]ramelteon. The Papp values for [14C]ramelteon, in the presence and absence of quinidine (a known inhibitor of P-glycoprotein), [3H]digoxin (a known substrate for P-glycoprotein), and DL-[3H]propranolol (a high permeability marker drug) were determined in both the apical-to-basolateral and basolateral-to-apical directions.

Papp for [14C]ramelteon from the apical to basolateral sides of the monolayer was similar to that from the basolateral to apical sides (27.3±5.3 x 10-6 and 28.5±2.1 x 10-6 cm/sec, respectively) and was higher than that for DL-[3H]propranolol (19.0±2.2 x 10-6 and 17.4±2.8 x 10-6 cm/sec, respectively) in either direction. Furthermore, Papp of [14C]ramelteon was not affected by quinidine.

Rat portal vein metabolism study:

Additionally, in vitro rat portal vein metabolism study was conducted to show the ramelteon gut absorption characteristics. [14C]ramelteon was injected into the jejunal loop at a dose of 1 mg/kg. Major component of radioactivity in the rat portal vein plasma was unchanged ramelteon (96, 93, 95, and 91% of the total radioactivity at 0-0.5, 0.5-1, 1-1.5, 1.5-2 hours, respectively). The results suggested that ramelteon is stable in the intestinal tract and not metabolized in the absorption processes prior to reaching the systemic circulation.

Dissolution profiles

The dissolution of the Phase II/III 4 mg tablet (reference formulation) was compared with that of the Phase I 4 mg tablet (test formulation). The differences between these 2 formulations were minor and included the [ ] used in the [ ] process and the quantity of [ ] in the tablet core. The dissolution conditions used were USP Apparatus II at 50 rpm and 37°C, in 900 mL of each of 3 different media (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). Dissolution is complete in minutes in all three media. The f_2 values for 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer were 57.9, 69.1, and 75.2, respectively, indicating that the dissolution profiles for the Phase I and Phase II/III formulations (4 mg tablets) were similar in each of the 3 test media.

Additionally, the dissolution profiles of the 4 and 8 mg tablets for the Phase I and Phase II/III, and to-be-marketed 8 mg tablet formulations were compared using water as medium. The Phase I and Phase II/III formulations exhibited similar and rapid dissolution, with more than of the label claim consistently dissolving within minutes.

Ultimately, the Applicant proposed the following dissolution method and specification: USP apparatus II at 50 rpm, 900 mL water with a Q of in minutes.

Formulation ingredient information

See *Section 2.1.1.* for list of ingredients for clinical and to-be-marketed formulations. The differences between the Phase I and Phase II/III formulations were very minor; the differences are in minimal amount of [ ] and [ ] the [ ] The performance between Phase I and II/III tablets are not expected.

The 8 mg commercial tablets are identical to the 8 mg Phase II/III tablets, except for the addition of [ ]. Again, the performance between Phase II/III and to-be-marketed tablets are not expected.

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/s/

David Lee
6/30/05 12:39:27 PM
BIOPHARMACEUTICS

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6/30/05 12:43:43 PM
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-782	Submission Date: 9/21/04
Submission Type; Code:	Original; 1S
Brand/Code Name:	[ ]
Generic Name:	Ramelteon (TAK-375)
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
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1 Executive Summary

Takeda Global Research & Development Center, Inc has submitted NDA 21-782 on 9/21/04 for approval for the treatment of insomnia [ ] The Applicant proposed to administer 8 mg once nightly within 30 minutes prior to bed time in all patients at least 18 years of age.

The main concept of this drug is to shorten the time to sleep onset and increasing sleep duration without producing side effects such as sedation, anxiolysis, muscle relaxation, and amnesia.

The "insomnia" treatment claim has been studied in 4 major clinical trials in subjects with transient insomnia and in subjects with chronic insomnia (short-term treatment (1 or 2 nights), long-term treatment (35 nights)). These studies were conducted in the sleep laboratory and in an outpatient setting. Endpoints were measured objectively by polysomnography (PSG) and measured subjectively by subject reports.

The Clinical Pharmacology and Biopharmaceutics studies assessed dose selection, absolute bioavailability, effect of food, special populations and drug-drug interactions. The Applicant claimed that ramelteon meets the BCS Classification 1 category. Thus, no bioequivalence studies comparing clinical and commercial formulations were submitted in the application.

The submitted Clinical Pharmacology and Biopharmaceutics information in this NDA package is adequate; however, a modification to the [ ] Package Insert is suggested.

1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II), the information contained in the NDA is acceptable, provided that a mutually satisfactory agreement can be reached between the Applicant and the Agency with respect to the language in the package insert (see section 3: Detailed Labeling Recommendations).

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

The Ramelteon (TAK-375) has been studied in doses ranging from 0.3 to 160 mg in 43 efficacy, safety, tolerability, pharmacodynamic, and pharmacokinetic clinical trials in the United States, Canada, Europe, and Japan. Doses ranging from 4 to 160 mg have been studied in safety and efficacy trials in the United States and Canada. Doses chosen for the pharmacokinetic and the Phase I pharmacodynamic studies were based on multiples of a 16 mg dose, which was the original planned therapeutic dose for humans based on the results of animal studies.

No Phase III population pharmacokinetic studies were conducted. No bioequivalence studies were conducted to compare clinical (Phases I and II/III) and to-be-marketed formulations. The Applicant claims that ramelteon meets BCS Classification 1 category. The Applicant's supporting data is discussed in Section 2.5. The Applicant's data have been forwarded to the BCS Committee, and the Committee has suggested studying ramelteon in vitro stability in simulated intestinal and gastric fluids. This recommendation has been communicated to the Applicant. Thus, the final determination will be pending further submission of data. The differences between the two formulations appear to be minor and supported by in vitro dissolution data, and it is expected that there will be no performance differences.

Ramelteon appears to have large inherent *in vivo* variability (observed standard deviation as large as 100%).

The absolute bioavailability of [ ] tablet is approximately 2% (range of 0.5% to 12%).

After IV administration, serum concentrations of ramelteon appeared to decline in a multi-phasic manner, with an arithmetic mean T1/2 of 1.9 hours. The CL and Vdss for ramelteon were 916 mL/min and 73.6 L, respectively.

After oral administration, less than 1% of ramelteon and M-II is excreted in urine and feces. M-II is present in concentrations 20-100 times higher than parent drug in human

serum. M-II appeared to decline in a mono-phasic manner, resulting in an arithmetic M-II mean T1/2 was approximately 2.6 hours. *In vitro*, M-II has approximately one-tenth and one-fifth the affinity of ramelteon for the human MT_1 and MT_2 receptors, respectively.

In vitro studies indicated that ramelteon is metabolized primarily by CYP1A2, and to a minor extent by the CYP2C subfamily and CYP3A4. M-II is metabolized further mainly by CYP3A4. *In vitro* rat portal vein study indicated that ramelteon is absorbed from the intestinal gut as an intact drug. *In vitro* Caco-2 cell information indicated that ramelteon absorption is not affected by P-glycoprotein receptors.

Ramelteon protein binding is approximately 82% and is independent of concentration. Ramelteon mostly binds to serum albumin. Ramelteon distributes into red blood cell approximately 25 %. M-II protein binding is approximately 70% and is independent of concentration.

Ramelteon and its metabolites exhibited linear pharmacokinetics in the dose range of 4 to 64 mg.

Sixty-four mg of ramelteon (eight fold higher dose than is sought for approval) did not prolong QT interval in a thorough QT study.

Ramelteon AUC(0-inf) and Cmax were 97% and 86% higher, respectively, and T1/2 was 66% longer in older subjects (63-79 years of age) compared with younger (18-34 years of age) subjects. M II AUC, Cmax and T1/2 were 30% and 13% higher, and 33% longer, respectively, in elderly compared with younger subjects.

Ramelteon AUC(0-inf) and Cmax were 32% and 19% higher, respectively, and T1/2 was 23% longer in women compared with men.

Generally there was no consistent change in individual subject ramelteon AUC and Cmax values on Day 8 with increasing severity in renal impairment. Ramelteon Cmax and AUC(0-τ) were not markedly different in subjects with mild to severe renal impairment compared to their healthy controls following multiple dosing.

Single and multiple dose administration of 16 mg ramelteon resulted in significant increases in exposure to ramelteon in subjects with mild hepatic impairment (3.5 to 3.6-fold higher AUCs) and moderate hepatic impairment (8.0 to 10.7-fold higher AUCs) relative to their corresponding healthy matched controls. Exposure to major metabolite M-II was only marginally increased in mildly and moderately hepatically impaired subjects relative to the respective healthy matched controls. Severe hepatic impairment group was not studied.

Ramelteon is not an inhibitor of 1A2, 2C19, 2D6, and 3A4 enzymes. Ramelteon is not an inducer of 1A2, 2C9 and 3A4 enzymes. According to *in vitro* CaCo-cell study and *in vivo* digoxin study, ramelteon is not a P-gp inhibitor.

Administration with high fat breakfast results in a 30% increase in AUC, 22% decrease in Cmax, and 1 hour increase in Tmax of remelteon. Due to the delay in absorption, remelteon should be administered without food. Food had little effect on M-II AUC(0-inf), but Cmax decreased 35%.

Ramelteon pharmacokinetic properties were not assessed in smokers; it is well known that smoking will induce CYP1A2 activity. Thus, it is possible that smokers may have lower ramelteon levels, making ramelteon less efficacious in this population. It is also noted that rifampin, a strong CYP inducer, drug interaction study showed significant decrease in ramelteon and M-II AUC and Cmax values; for rifampin, ramelteon is recommended not to be taken concomitantly due to uncertainty in dosage adjustment.

With respect to dosage adjustment, please see the following table. The Applicant claim that they recommend 'no dosage adjustment' based on the fact that ramelteon has a wide therapeutic index, adverse events observed in impairment or in drug-drug interaction studies are similar to that of administered ramelteon alone; the Applicant concluded that observed changes are not 'clinically significant.' Some of the Applicant's proposal is acceptable.

For elderly population, it is suggested that 4 mg dose may be safe and efficacious in this population. Food should not be taken with ramelteon; Tmax was prolonged with food.

Special Populations:

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 Moderate Severe Hemodialysis	 26 % ↓ 29 % ↑ 81 % ↑ 50 % ↓	 36 % ↓ 65 % ↑ 21 % ↑ 35 % ↓	 33 % ↑ 21 % ↓ 40 % ↑ 29 % ↓	 2 2 % ↑ ↔No change 9 % ↓	 No adjustment	
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 Moderate Severe	 258 % ↑ 967 % ↑ Not studied	 146 % ↑ 737 % ↑ Not studied	 29 % ↑ ↔ Not studied	 6 % ↓ 25 % ↓ Not studied	 No adjustment	

*Dosed for 7 days

Drug-Drug interaction studies:

Factor	Ramelteon AUC	Ramelteon Cmax	M II AUC	M II Cmax	Sponsor's proposal	**Agency's proposal**
1A2 inhibitor (fluvoxamine)	190-fold ↑	70-fold ↑	31 % ↑	60 % ↓		
3A4 inhibitor (ketoconazole)	84 % ↑	36 % ↑	93 % ↑	23 % ↑	No adjustment	
2C9 inhibitor (fluconazole)	52 % ↑	44 % ↑	200 % ↑	55 % ↑		**Use with Caution**
2C19 inhibitor (omeprazole)	30 % ↓	30 % ↓	29 % ↑	16 % ↑	No adjustment	**No adjustment**
2D6, 2C9, 2C19, 3A4 inhibitor (fluoxetine)	50 % ↑	40 % ↑	52 % ↑	17 % ↑	No adjustment	**No adjustment**
3A4 induction (rifampin)	80 % ↓	80 % ↓	89 % ↓	81 % ↓		
1A2 substrate (theophylline)	40 % ↑	35 % ↑	12 % ↑	↔	No adjustment	**No adjustment**
2D6 substrate (dextromethorphan)	↔	↔	↔	↔	No adjustment	**No adjustment**
Alcohol	47 % ↑	43 % ↑	10 % ↑	↔	No adjustment; but, use with caution	-

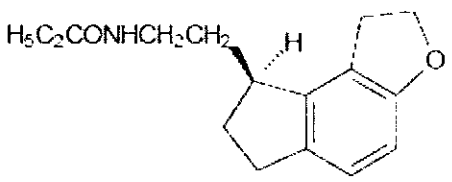
Overall, adequate data characterizing the Clinical Pharmacology and Biopharmaceutics aspects of [ ] IR tablets was provided.

2 QBR

2.1 General Attributes of the Drug

Ramelteon (TAK-375), (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl] propionamide, is developed as a sleep-promoting agent for the treatment of insomnia. The solubility of ramelteon in water is 0.21 mg/mL, and it is freely soluble in common organic solvents, such as benzyl alcohol, methanol, and dimethylsulfoxide. The chemical structure of ramelteon is presented below.

Chemical Structure of Ramelteon



2.1.1 What are the highlights of the chemistry and physical-chemical properties of ramelteon, and the formulation of ramelteon 8 mg tablets?

No bioequivalence studies were conducted to compare clinical and to-be-marketed formulations. The Applicant claims that ramelteon meets BCS Classification 1 category. The Applicant's supporting data is discussed in Section 2.5. The Applicant's data have been forwarded to the BCS Committee, and the Committee has suggested studying ramelteon in vitro stability in simulated intestinal and gastric fluids. This recommendation has been communicated to the Applicant. Thus, the final determination will be pending further submission of data. The differences between the two formulations appear to be minor and supported by in vitro dissolution data, and it is expected that there will be no performance differences.

Ramelteon is slightly sensitive to light and has a bitter taste. Therefore, a film coating was applied to the tablets, using conventional excipients. The Applicant stated that ramelteon meets the criteria for a BCS Class 1 drug, and in vivo bioequivalence studies were not conducted. See Section 2.5, General Biopharmaceutics for further discussion.

The differences between the Phase I and Phase II/III formulations were very minor; the differences are in minimal amount of [ ] The performance between Phase I and II/III tablets is not expected to be different. The 8 mg commercial tablets are identical to the 8 mg Phase II/III tablets, except for the addition of [ ] Again, the performance between Phase II/III and to-be-marketed tablets is not expected to be different.

Comparison of Investigational and Commercial Formulations: Overall Phases I, II/III, and Commercial formulations:

Component (mg/tablet)	Phase I Formulation	Phase II/III Formulation (a)	Commercial Formulation (b)	Function
Tablet core				
Ramelteon	0.1-10.0	4.0-32.0	8.0	
Starch	[ ]			
HPC				
Magnesium stearate				
Lactose monohydrate				
Film coating				
Hypromellose				
Copovidone				
PEG 8000				
Titanium dioxide				
Ferric oxide, yellow				
[ ]				
PEG 8000				
Printing ink				
				]
Other properties				
Total tablet weight (mg	137.0	135.0	135.0	
Strengths developed	0.1, 1, 4, 8, and 10	4, 8, 16, and 32	8	

Comparison of individual strengths used in Phases I, II/III, and Commercial formulations:

Table 2.b Comparison of Investigational and Commercial Formulations

	Formulation	Phase I Tablets				Phase II/III Tablets						Commercial Tablets (a)
	Strength	0.1 mg	1 mg	4 mg	8 mg	10 mg	4 mg	8 mg	16 mg	16mg (b)	32 mg	8 mg
Ingredient		Quantity per Tablet (mg)										
	Ramelteon	0.1	1.0	4.0	8.0	10.0	4.0	8.0	16.0	16.0	32.0	8.0
Tablet Core	Lactose monohydrate	[redacted]										
	Starch											
	Hydroxypropyl cellulose -											
	Hydroxypropyl cellulose -											
	Magnesium stearate											
Film Coating	Hypromellose	[redacted]										
	Polyethylene glycol 8000 -											
	Copovidone											
	Titanium dioxide											
	Ferric oxide, yellow											
	Polyethylene glycol 8000 -											
	Printing ink											
	TOTAL	137.0	137.0	137.0	137.0	137.0	135.0	135.0	135.0	135.0	135.0	135.0

(a) Used without imprinting for Phase III long-term safety study.
(b) Used only in Phase III long-term safety study.

2.1.2 What is the proposed mechanism of action?

Ramelteon is expected to have sleep-promoting activity, given its selectivity for MT_1 and MT_2 receptors; in vitro, ramelteon demonstrates high affinity and selectivity for human melatonin MT_1 or MT_2 receptors compared to the melatonin MT_3 receptor. Ramelteon also demonstrates full agonist activity relative to melatonin in cells expressing human MT_1 or MT_2 receptors.

In vitro, M-II has approximately one-tenth and one-fifth the affinity of ramelteon for the human MT_1 and MT_2 receptors, respectively. M-II has relatively weak affinity for the 5-HT_{2B} receptor (Ki = 1.75 µmol/L), but little affinity for other receptors, even at high concentrations of 10 µmol/L. M-II had no effect on the activity of several enzymes when tested in vitro at concentrations of 10 to 1000 µmol/L. M-II is present in concentrations 20-100 times higher than parent drug in human serum (e.g., see section 2.2.4.1. Absolute bioavailability: M-2 levels were 60 times higher than ramelteon; Japanese single dose ascending study: M-2 levels were 100 time higher than ramelteon information).

The contribution of M-II to the overall efficacy of ramelteon in vivo is not known since M-II was not administered directly to humans. However, it is reasonable to expect the same magnitude of efficacy if one considers the amount of concentration in vivo and taking the 1/10 and 1/5 the affinity toward MT1 and MT2 receptors (e.g. the magnitude is theoretically calculated by multiplying concentrations and affinity to receptors).

Ramelteon and its major metabolite, M-II, have negligible affinity (Ki greater than 10 μM) for the $GABA_A$ receptor complex, as well as for receptors that bind dopamine, serotonin, acetylcholine, glutamate, noradrenaline, and various neuropeptides, cytokines, and opiates. Therefore, ramelteon is not expected to produce the ancillary effects associated with the use of benzodiazepine receptor agonists, including sedation, anxiolysis, muscle relaxation, and amnesia.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosage and route of administration for [ ] ™ (ramelteon IR tablet) is 8 mg taken orally 30 minutes prior to bedtime.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials, and what is the basis for selecting the response endpoints?

[ ] was studied in randomized double-blind trials in subjects with chronic insomnia. One of the pivotal trials utilized a parallel design in which chronic insomnia adult subjects received a single nightly dose of the drug or matching placebo for 35 days. Polysomnography (PSG) was performed to measure sleep latency on the first two nights in each of weeks 1, 3, and 5 of treatment. The other pivotal trial utilized a three-arm crossover trial in which chronic insomnia elderly subjects received a single nightly dose of the drug or matching placebo in a sleep laboratory for two consecutive nights in each of the 3 study periods. PSG was performed.

[ ] was also studied in transient insomnia subjects in a parallel study design. Again, PSG was used as the primary method to measure sleep latency.

Endpoints (e.g., sleep latency, total sleep time, wake time after sleep onset, etc.) utilized in the clinical trials are measured by polysomnography (PSG). PSG is typically used in assessing drug treatment effect in insomnia clinical trials.

2.2.2 Are the active moieties in the serum and urine appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

See Section 2.6, Analytical Section for measurements of active moieties in the plasma and urine. In short, blood samples were obtained for determination of the pharmacokinetics of TAK-375. Serum concentrations of unchanged TAK-375 and its main metabolites (M-I, M-II, M-III, and M-IV) were measured using [ ]. At each time point venous blood were drawn, then allowed to stand at room temperature for approximately —

minutes and centrifuged [redacted] for [redacted] minutes to obtain the serum. The serum was stored at [redacted] until the assay was performed.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The Applicant stated that no consistent dose-response relationship was observed across the studies with respect to the efficacy of ramelteon. In Phases II and III, trials indicated that ramelteon doses (4 mg – 64 mg) were effective. Higher doses did not show any additional effectiveness; ramelteon may show a flat dose-response characteristic.

In Phases II and III, there were 6 double-blind, placebo-controlled studies conducted to establish the efficacy of ramelteon. The majority of subjects in each study were women (range: 52% - 77% across treatment groups). It should be noted that the insomnia is approximately 1.5 times more common in women than in men. The subjects studied in the ramelteon trials were similar to the actual patient population reporting insomnia.

Two Phase II studies were dose-ranging studies (PNFP002 and TL005) and other 4 studies were Phase III major trials:

Study (Phase)	Population	Model	N	Setting	Study Design	Doses (mg)	Duration of Double-Blind Treatment
Dose-finding studies							
PNFP002 (II)	Adult	Transient insomnia	375	Sleep laboratory	Parallel	16, 64	1 night
TL005 (II)	Adult	Chronic insomnia	107	Sleep laboratory	Crossover	4, 8, 16, 32	2 nights
Pivotal trials							
TL023 (III)	Adult	Transient insomnia	289	Sleep laboratory	Parallel	8, 16	1 night
TL021 (III)	Adult	Chronic insomnia	405	Sleep laboratory and outpatient	Parallel	8, 16	**35 nights**
TL017 (III)	**Elderly**	Chronic insomnia	100	Sleep laboratory	Crossover	4, 8	2 nights
TL025 (III)	**Elderly**	Chronic insomnia	829	Outpatient	Parallel	4, 8	**35 nights**

The Applicant stated that dose-finding studies revealed that all ramelteon doses were effective as measured by primary and secondary endpoints, latency to persistent sleep (LPS; statistically shorter with ramelteon) and total sleep time (TST; statistically longer with ramelteon), respectively (see below tables).

It is noted that, in PNFP002 study, there were occasional statistically significant differences were observed with respect to next-morning residual effects following treatment with ramelteon 64 mg.

Latency to Persistent Sleep (LPS) measure: Differences (minutes) between ramelteon and placebo

Study/Primary Efficacy Variable	Ramelteon Dose (mg)				
	4	8	16	32	64
PNFP002	--	--	-10.4*	--	-9.2*
TL005	-13.7*	-13.4*	-13.7*	-14.8*	--

*Statistically significant
--Not applicable

Total Sleep Time (TST) measure: Differences (Minutes) Between Ramelteon and Placebo

Study/Primary Efficacy Variable	Ramelteon Dose (mg)				
	4	8	16	32	64
PNFP002	--	--	14.0*	--	11.4*
TL005	10.7*	12.6*	10.9*	17.9*	--

*Statistically significant
--Not applicable

In Phase III trials, the Applicant reported the following PSG data looking at the time to sleep onset (LPS) and the duration of sleep (TST); see below tables.

Ramelteon Phase III Studies: Sequences of Efficacy Variables

	Study			
	TL017	TL021	TL023	TL025
Primary variable	LPS[#]	LPS	LPS	sSL[$]
First secondary variable	TST[^]	TST	TST	sTST[•]
Second secondary variable	Sleep quality	Sleep quality	Sleep quality	Sleep quality

[#]Latency to Persistent Sleep (LPS)
[$]Subjective sleep latency
^Total Sleep Time (TST)
[•]Subjective total sleep time

Latency to Persistent Sleep (LPS) measure: Differences (minutes) between ramelteon and placebo

Study/Primary Efficacy Variable	Ramelteon Dose (mg)				
	4	8	16	32	64
LPS					
TL023	--	-7.6*	-4.9	--	--
TL021					
Week 1	--	-15.7*	-18.9*	--	--
Week 3	--	-12.9*	-17.6*	--	--
Week 5	--	-11.0*	-12.9*	--	--
TL017 (Elderly)	-9.7*	-7.6*	--		
sSL TL025 (Elderly)					
Week 1	-8.3*	-8.3*	--	--	--
Week 3	-4.5	-9.0*	--	--	--
Week 5	-7.1*	-12.8*	--	--	--

*Statistically significant
#Subjective sleep latency
--Not applicable

Total Sleep Time (TST) measure: Differences (Min.) Between Ramelteon and Placebo

Study/Primary Efficacy Variable	Ramelteon Dose (mg)				
	4	8	16	32	64
TST					
TL023	--	17.1*	13.5*	--	--
TL021					
Week 1	--	19.0*	22.4*	--	--
Week 3	--	5.3	11.8	--	--
Week 5	--	5.6	7.4	--	--
TL017 (Elderly)	9.0*	11.5*	--	--	--
sTST# TL025 (Elderly)					
Week 1	10.8*	7.3	--	--	--
Week 3	11.7*	7.8	--	--	--
Week 5	7.4	4.3	--	--	--

*Statistically significant
#Subjective total sleep time
--Not applicable

Looking at the Phase II dose-ranging studies, 4 mg ramelteon dose may be efficacious in adults. However, in Phase III studies the Applicant only tested 8 and 16 mg in adults. With respect to elderly studies, 4 mg ramelteon dose should be effective in elderly population.

2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In general, drugs utilized to treat insomnia showed increased treatment-emergent adverse events (e.g., somnolence) with increasing dose. Ramelteon is no exception. Looking at the over all adverse events, ramelteon displays this trend. The number of subjects exposed to ramelteon and placebo is summarized by dose below:

		Ramelteon						All Doses of Ramelteon
	Placebo	<4 mg	4 mg	8 mg	16 mg	32 mg	64 mg	
Phase I to Phase III studies	1370	20	511	1250	1961	169	209	3594
Chronic insomnia (placebo-controlled) studies	897	0	486	896	528	105	0	1599
Studies in healthy volunteers	408	20	25	106	411	64	209	725
Long-term safety study	0	0	0	248	965	0	0	1213
Drug-interaction studies	50	0	0	0	136	161	0	297
Disease-interaction studies	72	0	0	0	170	20	0	170
Japanese studies	55	24	8	36	40	27	0	124

Treatment-emergent adverse events were clustered into three groups: Phase I to Phase III studies (>4 mg – 64 mg), the chronic insomnia studies (4 – 32 mg), and long-term open-label elderly subject study (Study TL022; elderly subjects who received 8 or 16 mg for a minimum of 3 days each week for up to 1 year). The Phase I to Phase III studies represent the largest set of subjects exposed to ramelteon, and the chronic insomnia studies represent the subjects most closely simulating the expected patient population that will use ramelteon.

It should be noted that ramelteon 32 mg and 64 mg groups had fewer subjects than other groups, and exposures at doses higher than 16 mg were generally shorter than exposures at lower doses (no more than 7 days or nights).

1. Adverse events reported for 1% or more subjects who received ramelteon: Phase I to III Studies

MedDRA Preferred Term	Placebo (n=1370)	Ramelteon <4 mg (n=20)	Ramelteon 4 mg (n=511)	Ramelteon 8 mg (n=1250)	Ramelteon 16 mg (n=1961)	Ramelteon 32 mg (n=169)	Ramelteon 64 mg (n=209)	All Doses of Ramelteon (n=3594)
Any adverse event	558 (40.7%)	16 (80.0%)	191 (37.4%)	554 (44.3%)	928 (47.3%)	56 (33.1%)	74 (35.4%)	1728 (48.1%)
Headache NOS	92 (6.7%)	2 (10.0%)	22 (4.3%)	86 (6.9%)	175 (8.9%)	10 (5.9%)	15 (7.2%)	299 (8.3%)
Somnolence	45 (3.3%)	8 (40.0%)	13 (2.5%)	57 (4.6%)	185 (9.4%)	4 (2.4%)	17 (8.1%)	273 (7.6%)
Fatigue	26 (1.9%)	6 (30.0%)	6 (1.2%)	43 (3.4%)	84 (4.3%)	2 (1.2%)	10 (4.8%)	148 (4.1%)
Dizziness	44 (3.2%)	1 (5.0%)	20 (3.9%)	52 (4.2%)	59 (3.0%)	0	2 (1.0%)	133 (3.7%)
Nausea	31 (2.3%)	0	11 (2.2%)	36 (2.9%)	61 (3.1%)	2 (1.2%)	4 (1.9%)	110 (3.1%)
Nasopharyngitis	35 (2.6%)	0	8 (1.6%)	22 (1.8%)	54 (2.8%)	1 (0.6%)	1 (0.5%)	86 (2.4%)
Insomnia exacerbated	23 (1.7%)	0	7 (1.4%)	36 (2.9%)	31 (1.6%)	0	0	74 (2.1%)
Upper respiratory tract infection NOS	26 (1.9%)	0	4 (0.8%)	27 (2.2%)	36 (1.8%)	3 (1.8%)	2 (1.0%)	72 (2.0%)
Diarrhea NOS	24 (1.8%)	1 (5.0%)	5 (1.0%)	22 (1.8%)	28 (1.4%)	1 (0.6%)	3 (1.4%)	59 (1.6%)
Myalgia	12 (0.9%)	0	15 (2.9%)	20 (1.6%)	17 (0.9%)	1 (0.6%)	0	53 (1.5%)
Pharyngitis	16 (1.2%)	0	4 (0.8%)	16 (1.3%)	23 (1.2%)	4 (2.4%)	4 (1.9%)	50 (1.4%)
Depression	8 (0.6%)	0	10 (2.0%)	20 (1.6%)	13 (0.7%)	0	1 (0.5%)	44 (1.2%)
Dysgeusia	19 (1.4%)	0	8 (1.6%)	24 (1.9%)	6 (0.3%)	0	1 (0.5%)	38 (1.1%)
Dry mouth	22 (1.6%)	0	7 (1.4%)	17 (1.4%)	14 (0.7%)	0	2 (1.0%)	39 (1.1%)
Back pain	12 (0.9%)	0	4 (0.8%)	13 (1.0%)	20 (1.0%)	1 (0.6%)	0	38 (1.1%)
Dyspepsia	7 (0.5%)	0	4 (0.8%)	12 (1.0%)	19 (1.0%)	4 (2.4%)	0	39 (1.1%)
Constipation	14 (1.0%)	0	4 (0.8%)	9 (0.7%)	12 (0.6%)	9 (5.3%)	7 (3.3%)	36 (1.0%)
Pruritus NOS	20 (1.5%)	0	8 (1.6%)	10 (0.8%)	4 (0.2%)	8 (4.7%)	7 (3.3%)	36 (1.0%)
Urinary tract infection NOS	17 (1.2%)	0	4 (0.8%)	11 (0.9%)	18 (0.9%)	1 (0.6%)	1 (0.5%)	35 (1.0%)

Looking at Phase I to III studies, the most commonly occurring adverse events were headache, somnolence, fatigue, dizziness, nausea, nasopharyngitis, insomnia exacerbated, and upper respiratory tract infection not otherwise specified (NOS). In each treatment group, more than 50% of subjects reporting events had events that were considered by the investigator to be drug related (60.1% of subjects). Looking at ramelteon doses of 4 to 16 mg, the above table indicated that there appeared to be a dose relationship for increased AEs with increasing dose.

2. Adverse events reported for 1% or more of 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%)

Again it should be noted that 32 mg ramelteon group had the fewest subjects. Adverse events with the highest incidences included dizziness, exacerbated insomnia, fatigue, nausea, myalgia, nasopharyngitis, depression, and dysgeusia. Again, looking at 4 – 16 mg ramelteon doses, there appeared to be a dose relationship for increased AEs with increasing dose.

3. Adverse events reported for 1% or more subjects who received ramelteon in Study TL022: interim results (elderly subjects who received 8 or 16 mg for a minimum of 3 days each week for up to 1 year)

The Applicant stated that 29 elderly subjects are treated to date. The mean length of exposure in this study is 102 days per subject receiving 8 mg, and 97 days per subject receiving 16 mg. Again, there appeared to be a dose relationship for increased AEs with increasing dose.

MedDRA Preferred Term	Ramelteon 8 mg (n=248)	Ramelteon 16 mg (n=965)	All Doses of Ramelteon (n=1213)
Somnolence	18 (7.3%)	69 (7.2%)	87 (7.2%)
Headache NOS	5 (2.0%)	75 (7.8%)	80 (6.6%)
Nasopharyngitis	6 (2.4%)	39 (4.0%)	45 (3.7%)
Fatigue	6 (2.4%)	35 (3.6%)	41 (3.4%)
Dizziness	10 (4.0%)	30 (3.1%)	40 (3.3%)
Upper respiratory tract infection NOS	9 (3.6%)	31 (3.2%)	40 (3.3%)
Nausea	10 (4.0%)	27 (2.8%)	37 (3.1%)
Diarrhea NOS	7 (2.8%)	19 (2.0%)	26 (2.1%)
Sinusitis NOS	1 (0.4%)	17 (1.8%)	18 (1.5%)
Arthralgia	7 (2.8%)	10 (1.0%)	17 (1.4%)
Influenza	4 (1.6%)	13 (1.3%)	17 (1.4%)
Urinary tract infection NOS	5 (2.0%)	12 (1.2%)	17 (1.4%)
Pharyngitis	3 (1.2%)	12 (1.2%)	15 (1.2%)
Lethargy	5 (2.0%)	9 (0.9%)	14 (1.2%)
Blood cortisol decreased	4 (1.6%)	10 (1.0%)	14 (1.2%)
Back pain	2 (0.8%)	10 (1.0%)	12 (1.0%)
Muscle cramps	3 (1.2%)	10 (1.0%)	13 (1.1%)
Insomnia exacerbated	4 (1.6%)	8 (0.8%)	12 (1.0%)

2.2.3.3 Does ramelteon prolong the QT interval?

Sixty-four mg of ramelteon (eight fold higher dose than is sought for approval) did not prolong QT interval in a thorough QT study.

The primary objective of the thorough QT study TL040(randomized, single-blind, 4-sequence, 4-period, crossover, active- and placebo-controlled) in healthy men and women was to evaluate the effect of multiple 32 and 64 mg doses of ramelteon on QTc intervals; Moxifloxacin was used as the active control. The pharmacokinetic profile of ramelteon was also assessed.

Ramelteon 32 and 64 mg for 6 days did not prolong QT intervals whereas moxifloxacin 400 mg administered QD for 6 days resulted in a statistically significant prolongation.

Endpoint Visit Treatment	Least-Squares Mean (SE)	Comparison to Placebo		Comparison to Moxifloxacin 400 mg	
		Estimate	P-value	Estimate	P-value
Change from Baseline in Mean QTcF Interval					
Day 1					
Placebo	-2.0 (0.85)				
Ramelteon 32 mg	-1.7 (0.85)	0.3 (0.98)	0.9769	-8.2 (0.99)	<0.0001 (a)
Ramelteon 64 mg	-1.3 (0.85)	0.7 (0.99)	0.8294	-7.9 (0.98)	<0.0001 (a)
Moxifloxacin 400 mg	6.5 (0.85)	8.5 (0.98)	<0.0001 (a)		
Day 6					
Placebo	-1.1 (0.83)				
Ramelteon 32 mg	-3.8 (0.83)	-2.6 (0.81)	0.0042 (b)	-11.8 (0.81)	<0.0001 (a)
Ramelteon 64 mg	-3.1 (0.83)	-2.0 (0.81)	0.0418 (b)	-11.2 (0.81)	<0.0001 (a)
Moxifloxacin 400 mg	8.0 (0.83)	9.2 (0.81)	<0.0001 (a)		

Source: Table 14.2.1.6.
SE indicates Standard Error.
(a) P<0.0001
(b) P<0.05.

Additionally, correlation of QTcF intervals (msec) versus serum ramelteon and M-II concentrations was examined by scatter plots and there was no apparent correlation between QTcF intervals and ramelteon or M-II concentrations.

Correlation Plots:

Figure 11.f Scatter Plot of QTcF Interval versus Serum Concentration of Ramelteon on Day 5

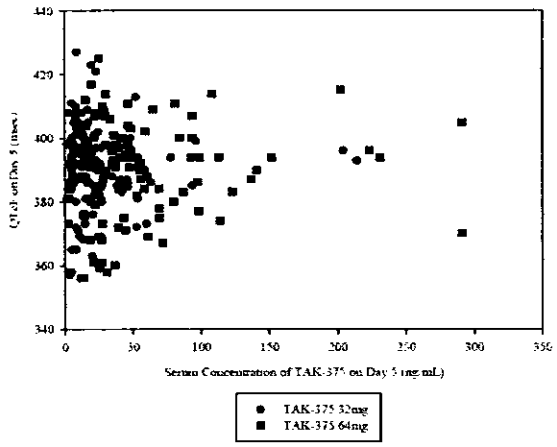
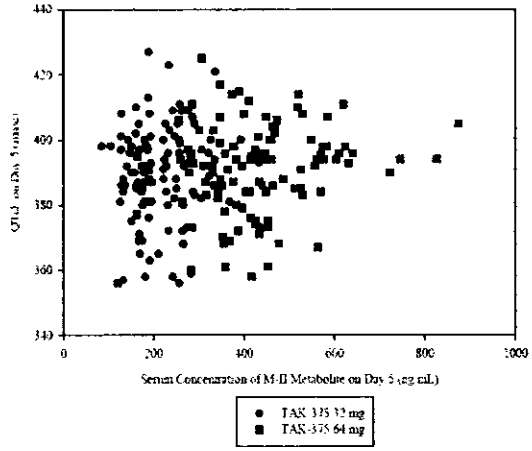


Figure 11.g Scatter Plot of QTcF Interval versus Serum Concentration of M-II or Day 5



2.2.3.4 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

It is suggested that elderly should administered ½ of adult dose, 4 mg. (See Elderly section, 2.2.3.1.)

Ramelteon AUC(0-inf) and Cmax were 97% and 86% higher, respectively, and T1/2 was 66% longer in older subjects (n=24, equal number of men and women; 63 - 79 years of age) compared with younger (n=24, equal number of men and women; 18-34 years of age) subjects. M II AUC, Cmax and T1/2 were 30% and 13% higher, and 33% longer, respectively, in elderly compared with younger subjects. Typically elderly (> 65 years of age) subjects may need ½ of that of the adult dose drugs to treat insomnia. Ramelteon elderly PD data indicated that this trend is also seen for ramelteon. However, the Applicant did not propose to administer ½ of adult dose in elderly subjects. From PD studies, it appears that ½ of adult dose should be used in elderly.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

2.2.4.1 Absorption

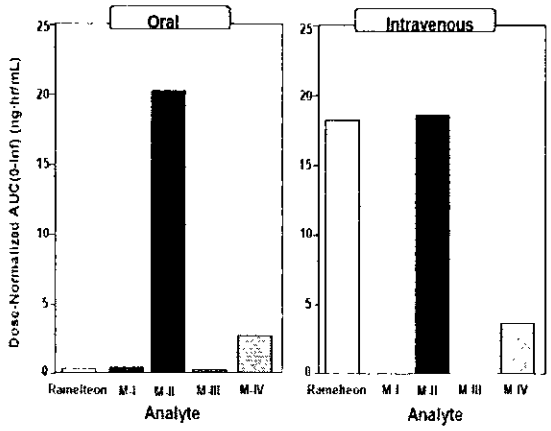
In vitro rat portal vein study indicated that ramelteon is absorbed from the intestinal gut as an intact drug. *In vitro* Caco-2 cell information indicated that ramelteon absorption is not affected by P-glycoprotein receptors.

Absolute bioavailability

The absolute bioavailability of [ ] tablet was 1.8% (range of 0.5% to 12%). This low bioavailability is due to extensive first-pass metabolism and not because of limited absorption. After IV administration, serum concentrations of ramelteon appeared to decline in a multi-phasic manner, with an arithmetic mean T1/2 of 1.9 hours for the terminal phase. The CL and Vdss for ramelteon were 916 mL/min and 73.6 L, respectively; the high Vdss suggests that ramelteon may distribute into tissues. After oral administration, the median Tmax was 0.75 hours. M-I and M-III were not measurable in serum after IV dosing. M-II was the predominant ramelteon metabolite detected in serum after administration of both the oral and IV dosing.

After the IV dose, dose-normalized $AUC_{(0\text{-}inf)}$ was similar for both compounds (see below). However, after the oral dose, dose-normalized $AUC_{(0\text{-}inf)}$ was approximately 60-fold higher for M-II than for ramelteon. These data suggest that orally administered ramelteon undergoes extensive first-pass metabolism.

Metabolic Composition of Ramelteon Administered Orally and IV in the Fasted State



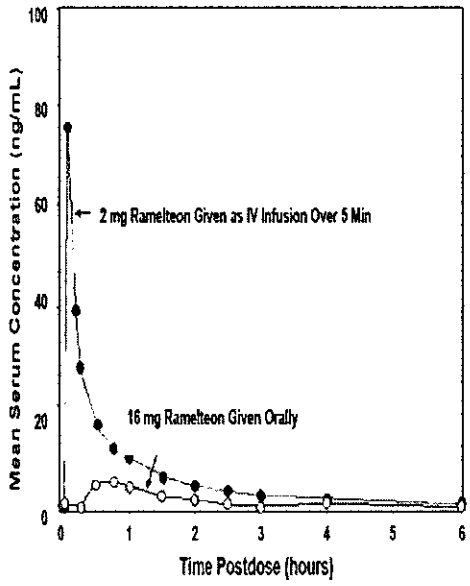
M-II appeared rapidly in serum, with a median Tmax of 1 hour after oral administration and 0.5 hours after IV administration. Serum concentrations of M-II appeared to decline in a mono-phasic manner, resulting in an arithmetic mean T1/2 of approximately 2.6 hours for both the oral and IV doses.

After the oral dose, the inter-subject variability in dose-normalized AUC(0-inf) and Cmax was lower for M-II (CV of 37% and 32%, respectively) than for ramelteon.

Overall PK parameters: (t1/2 – geometric means):

	Parameter	Tablet (16 mg) (N=18)	IV infusion (2 mg) (N=20)
TAK-375	$AUC_{(0-\infty)}$	0.325 (103)	18.2 (14.6)
	C_{max} (ng/mL)	3.89 (122)	69.8 (51.9)
	t_{max}[a] (h)	0.750 (0.500-1.50)	0.0833 (0.0667-0.167)
	$t_{1/2}$ (h)	1.09 (22.1)	1.80 (50.2)
M-I	$AUC_{(0-\infty)}$	0.507 (27.8)[b]	NC
	C_{max} (ng/mL)	6.26 (37.8)	0.539 (42.6)
	t_{max}[a] (h)	0.883 (0.250-2.00)	0.500 (0.250-0.750)[b]
	$t_{1/2}$ (h)	0.634 (27.4)[b]	NC
M-II	$AUC_{(0-\infty)}$	18.9 (37.0)	18.0 (40.8)
	C_{max} (ng/mL)	93.7 (31.8)	8.78 (32.4)
	t_{max}[a] (h)	1.00 (0.500-3.00)	0.500 (0.167-1.50)
	$t_{1/2}$ (h)	2.51 (31.3)	2.41 (30.0)
M-III	$AUC_{(0-\infty)}$	0.308 (36.4)[c]	NC
	C_{max} (ng/mL)	1.33 (83.0)	<0.500 (NC)
	t_{max}[a] (h)	0.833 (0.500-1.50)[c]	NC
	$t_{1/2}$ (h)	1.45 (24.3)[c]	NC
M-IV	$AUC_{(0-\infty)}$	3.39 (30.1)	4.69 (9.65)[d]
	C_{max} (ng/mL)	9.17 (29.1)	0.893 (28.3)
	t_{max}[a] (h)	1.25 (0.750-4.00)	0.875 (0.500-4.00)
	$t_{1/2}$ (h)	3.87 (19.5)	5.42 (16.7)[d]

Geometric mean (CV%) data are presented
[a] Median (min-max)
[b] N = 16
[c] N = 6
[d] N = 4
N = Number of subjects studied
(norm) = Normalised for dose
NC = Not calculated



2.2.4.2 Distribution

Ramelteon was distributed into red blood cells at 26.5%, 24.8%, and 25.3% at 0.01, 0.1, and 1 µg/mL, respectively. The protein-binding results were 83.3%, 81.1%, and 81.9% in human serum, and 68.8%, 71.9%, and 71.6% in human serum albumin at 0.01, 0.1, and 1 µg/mL, respectively, and were independent of concentration.

The M-II protein-binding results were 79.1%, 77.1%, and 76.5%, at 0.01, 0.1, and 1 µg/mL, respectively, and were independent of concentration.

2.2.4.3 Mass Balance

Comparison of blood and serum radioactivity concentrations indicated little uptake of ramelteon and its metabolites into blood cells. Total radioactivity mean ratio of whole

blood to serum remained relatively constant up to 24 hours post-dose and ranged from 0.57 to 0.73.

The principal route of excretion of total radioactivity was in urine (84%); fecal radioactivity recovery accounted for an additional 4% of the dose. These urine and fecal values result in a mean recovery of 88%. Of the 4% radioactivity in feces, less than 1% of the dose recovered in feces was due to ramelteon.

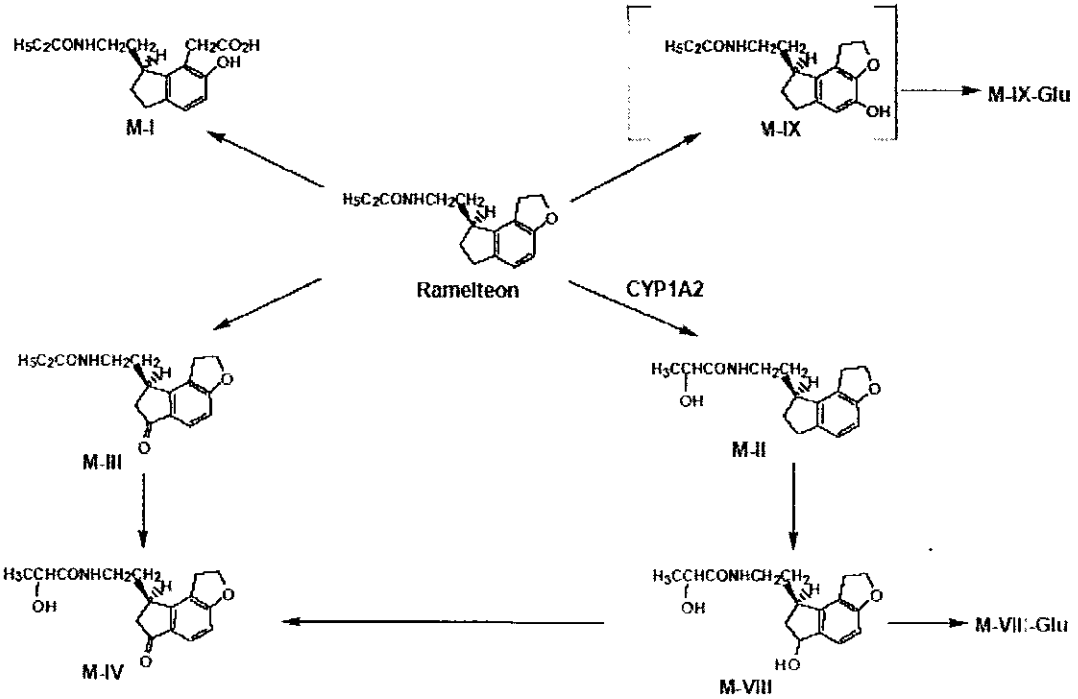
The AUC(0-inf) of ramelteon and metabolites I through IV combined amounted to approximately 13% of the excreted total radioactivity. The remaining radioactivity in serum was eliminated slowly from systemic circulation, resulting in a prolonged T1/2 (112 hours) for total radioactivity. The majority of the total radioactivity was excreted within 24 hours (range 58 – 62 %), followed by 12% to 26% total radioactivity excretion in 24 – 168 hours.

Ramelteon was present in serum at 20 minutes post-dose and at 1 hour, but concentrations declined over time and were undetectable by 4 hours.

At 20 minutes post-dose, M-II and a glucuronide conjugate of mono-hydroxylated parent compound (M-IX-Glu) were the main circulating metabolites, and accounted for 30% and 21% of serum radioactivity, respectively. At 4 hours post-dose, M-II and a glucuronide conjugate of dihydroxylated ramelteon (M-VIII-Glu) were the main circulating metabolites in serum and accounted for approximately 57% of total serum radioactivity.

Proposed ramelteon metabolic profile:

Ramelteon is extensively metabolized via 1A2, 2C9 and 3A4 enzymes.



In vitro hepatic microsome metabolism study (comparison of mice, rats, dogs, monkeys, and humans) revealed that no metabolites unique to humans were identified.

In other *in vitro* metabolism studies, CYP1A1, CYP1A2, CYP2C9, CYP2D6, and CYP3A4 were identified as the CYP isozymes involved in the biotransformation of ramelteon; however, only CYP1A2, CYP2C9, and CYP3A4 showed significant activity, suggesting that CYP1A2, CYP2C9, and CYP3A4 are involved in the hepatic metabolism of ramelteon. Enzyme CYP1A2 was the main isozyme involved in the metabolism of ramelteon to M-II. Enzyme CYP3A4 was involved mainly in the metabolism of M-II. More than 94% of M-II formed by the human hepatocytes was the 2*S*,8*S*-diastereomer.

In vitro induction study revealed that ramelteon very weakly induced CYP3A activity at 30 µmol/L. Compared with rifampicin, the induction activity of ramelteon was only 7% to 18% to that of rifampicin. M-II did not induce CYP3A activity at concentrations up to 30 µmol/L.

In vitro inhibition study revealed that ramelteon showed no inhibitory effects at 1 and 10µmol/L. The estimated IC50 ranges for ramelteon on CYP2C8, CYP2C19, and CYP3A4 activities were greater than 10 µmol/L (2.6 µg/mL). Comparing to the observed Cmax in the clinical setting, this concentration is more than 400-fold greater than typical ramelteon Cmax observed in subjects (~5.8 ng/mL). The overall information indicated that no *in vivo* drug interactions on CYP-mediated metabolism are expected with therapeutic doses of ramelteon.

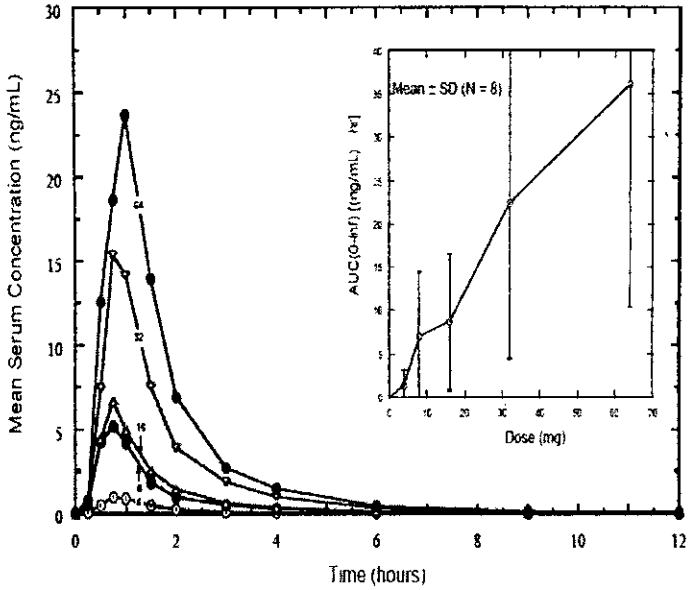
2.2.4.4 **What are the single dose and multiple dose PK parameters?**

Ramelteon and its metabolites exhibited linear pharmacokinetics in the dose range of 4 to 64 mg.

Single dose PK parameters: 4, 8, 16, 32, and 64 mg

Healthy subjects (9 men and 3 women per group; 7 men and 2 women were assigned to active group) were randomized to received single doses of ramelteon 4, 8, 16, 32, and 64 mg or placebo; all doses were administered after a 10-hour fast. The results indicated that ramelteon and its metabolites exhibited linear pharmacokinetics.

Healthy subjects dose proportionality of ramelteon at 4, 8, 16, 32, and 64 mg:



Dose- Normalized Pharmacokinetic Parameters for ramelteon:

Dose-Normalized Parameter	TAK-375					
	4.0 mg	8.0 mg	16.0 mg	32.0 mg	64.0 mg	p-value
AUC_{0-t} (hr•ng/mL)						
N	6	6	6	6	6	0.2148
Mean	0.3144	0.8515	0.5342	0.6963	0.5608	
SD	0.4325	0.9325	0.4905	0.5644	0.4011	
AUC_{0-inf} (hr•ng/mL)						
N	6	6	7	6	6	0.5494
Mean	0.4264	0.8688	0.6174	0.7031	0.5640	
SD	0.4872	0.9373	0.4600	0.5656	0.4019	
C_{max} (ng/mL)						
N	6	6	6	6	6	0.5911
Mean	0.2864	0.7165	0.4323	0.5441	0.4041	
SD	0.3119	0.6974	0.3324	0.4127	0.3105	

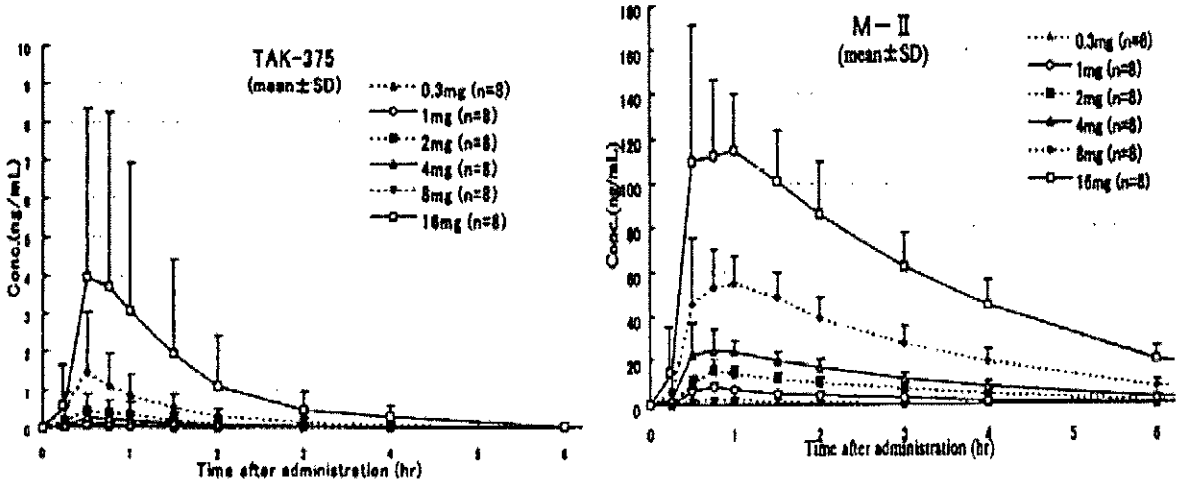
Ramelteon CL/F values were large, most likely due to its low absolute oral bioavailability. CLr and Fe% remained relatively constant across doses for ramelteon and its metabolites. Tmax, elimination rate constant, and T1/2 remained relatively constant for both men and women across dose groups.

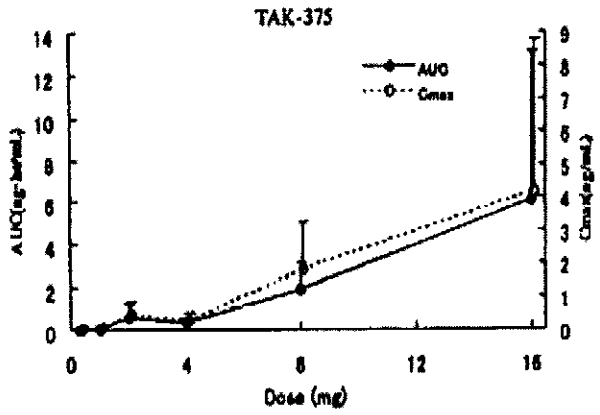
Women generally exhibited higher AUC and Cmax than men; however, due to a small number of women per dose group, a gender effect cannot be determined from this study:

Gender	TAK-375				
Parameter	4.0 mg	8.0 mg	16.0 mg	32.0 mg	64.0 mg
Males					
AUC_{0-t} (hr•ng/mL)					
N	6	6	6	6	6
Mean	1.529	3.783	6.168	22.845	23.267
AUC_{0-inf} (hr•ng/mL)					
N	4	6	5	6	6
Mean	2.295	3.892	7.490	23.047	23.456
C_{max} (ng/mL)					
N	6	6	6	6	6
Mean	1.338	3.082	5.848	17.052	16.432
Females					
AUC_{0-t} (hr•ng/mL)					
N	2	2	2	2	2
Mean	0.443	15.899	15.686	20.593	73.760
AUC_{0-inf} (hr•ng/mL)					
N	2	2	2	2	2
Mean	0.527	16.125	15.847	20.851	74.016
C_{max} (ng/mL)					
N	2	2	2	2	2
Mean	0.568	13.680	10.125	18.485	54.150

Japanese single dose PK parameters: 0.3, 1, 2, 4, 8, and 16 mg

Japanese healthy men were administered with ramelteon 0.3, 1, 2, 4, 8, and 16 mg single dose. Subjects were randomized into 4 groups of 12 subjects each and then randomized in a 2:1 ratio to receive single doses of either ramelteon or placebo. The results indicated that fasting Cmax and AUC of ramelteon showed high inter-subject variability, while M-II parameters showed less inter-subject variability. Mean ramelteon and M-II Cmax increased in an approximately dose-dependent manner. M-II peak concentrations were 30 to 100 times higher than ramelteon.





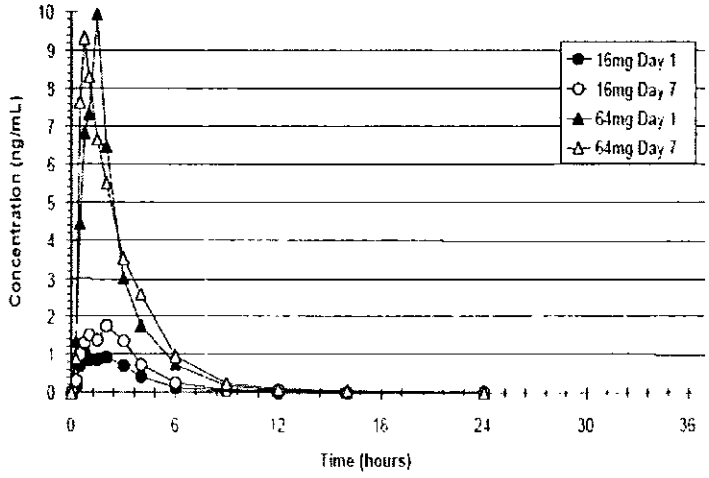
The results from this study indicated that ramelteon exhibited dose proportionality.

Multiple dose PK parameters: 16 mg QD or 64 mg QD for 7 days

Healthy subjects (17 men and 3 women in active and 3 men and 1 woman in placebo) were randomized to received ramelteon 16 mg QD for 7 nights during the first treatment period and ramelteon 64 mg QD for another 7 nights during the second treatment period, or placebo during both treatment period. All doses were administered 3 hours after a standard evening meal, which approximates conditions of use.

The results indicated that steady state was attained for both doses by Day 4. Median Tmax was approximately 1 hour on Days 1 and 7 at both doses. Median T1/2 of parent drug was approximately 75 minutes on Days 1 and 7 at both doses. Trough concentrations were not measurable after multiple doses. Ramelteon AUC values were 40% and 27% higher on Day 7 than on Day 1 at 16 and 64 mg, Respectively.

Exposure to Ramelteon on Days 1 and Day 7: After Dosing With Ramelteon 16 or 64 mg QD:

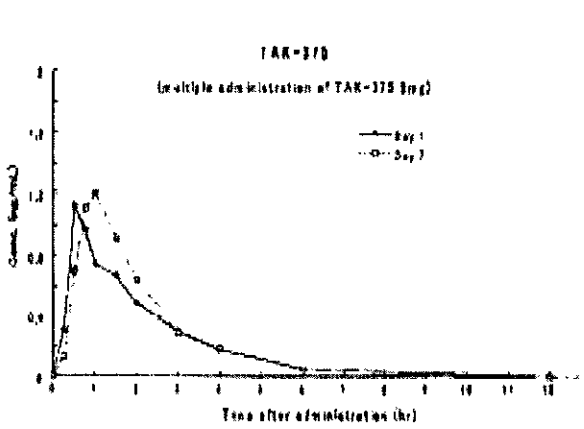


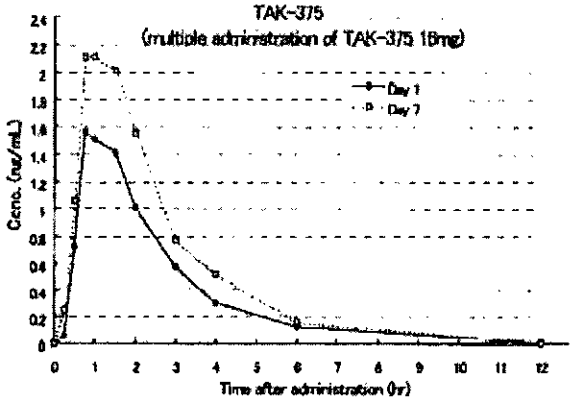
Japanese multiple dose PK parameters: 8 mg QD or 64 mg QD for 7 days

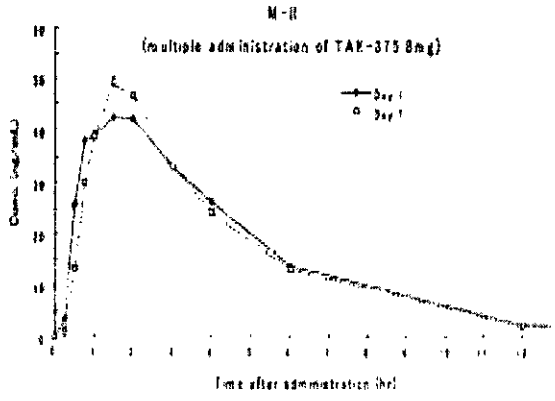
Japanese healthy men (8 men per group) received either ramelteon 8 mg QD for 7 days, or received ramelteon 16 mg QD for 7 days. The remaining 4 subjects in each group received placebo. All doses were administered 3 hours after the evening meal (2 hours before bedtime).

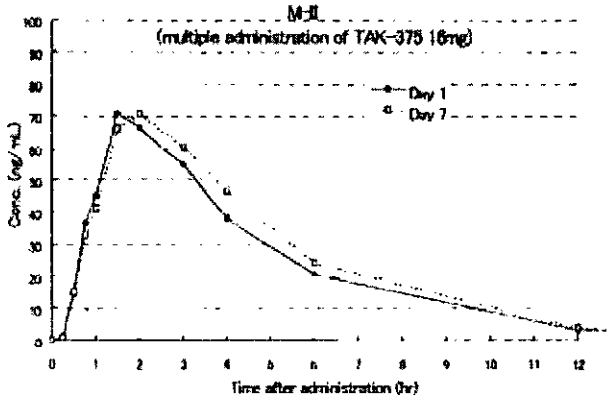
Cmax and AUC of ramelteon showed high inter-subject variability as observed previously in a Japanese single-dose study. Mean Cmax and AUC(0-24hr) for ramelteon and M-II increased in a dose-dependent manner. M-II peak concentrations were 30 to 40 times higher, and overall exposure was 60 to 100 times higher than ramelteon.

Cmax and AUC values for ramelteon on Day 7 were 31% and 16% higher, respectively, than on Day 1 after 8 mg QD dosing, and 19% and 25% higher, respectively, after 16 mg QD dosing. However, trough levels were below the lower limit of quantitation on Day 7 at both doses.









Dose	Time points of measurement	Compounds	AUC_{0-24} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ 1-compartment	$t_{1/2}$ 2-compartment*
8mg/day	Day 1	TAK-375	2.34 ± 1.01(8)	1.39 ± 1.05(8)	1.31 ± 0.84(8)	1.08 ± 0.23 (5)	1.84 ± 0.15 (2)
		M-I	3.53 ± 0.59(8)	2.64 ± 1.24(8)	1.16 ± 0.38(8)	-	-
		M-II	234.79 ± 62.20(8)	54.18 ± 21.20(8)	1.53 ± 0.80(8)	2.26 ± 0.42 (6)	2.58 ± 0.27 (2)
		M-IV	44.97 ± 8.67(8)	5.87 ± 1.00(8)	2.25 ± 1.30(8)	4.13 ± 0.90(8)	-
	Day 7	TAK-375	2.64 ± 1.40(8)	1.47 ± 1.03(8)	1.09 ± 0.38(8)	0.92 ± 0.31 (6)	1.69 ± 0.15 (2)
		M-I	3.74 ± 1.05(8)	2.76 ± 0.97(8)	1.19 ± 0.35(8)	-	-
		M-II	229.07 ± 66.03(8)	54.15 ± 10.53(8)	1.53 ± 0.54(8)	2.05 ± 0.54 (6)	2.75 ± 0.09 (2)
		M-IV	42.29 ± 8.35(8)	5.83 ± 0.48(8)	1.69 ± 0.37(8)	4.12 ± 0.88(8)	-
16mg/day	Day 1	TAK-375	4.23 ± 6.45(8)	1.85 ± 2.91(8)	1.22 ± 0.47(8)	1.25 ± 0.25 (7)	2.06 (1)
		M-I	7.66 ± 2.09(8)	4.37 ± 1.23(8)	1.53 ± 0.47(8)	-	-
		M-II	339.48 ± 124.17(8)	75.58 ± 24.39(8)	1.72 ± 0.65(8)	2.12 ± 0.36(8)	-
		M-IV	92.65 ± 23.24(8)	11.52 ± 2.93(8)	2.38 ± 0.69(8)	3.88 ± 0.68(8)	-
	Day 7	TAK-375	6.08 ± 9.46(8)	2.42 ± 3.63(8)	1.31 ± 0.46(8)	1.32 ± 0.61 (7)	1.96 (1)
		M-I	8.22 ± 1.83(8)	4.19 ± 1.14(8)	1.56 ± 0.72(8)	-	-
		M-II	380.39 ± 148.19(8)	76.60 ± 23.17(8)	2.00 ± 0.85(8)	2.17 ± 0.41 (8)	-
		M-IV	98.40 ± 29.82(8)	11.48 ± 3.13(8)	2.38 ± 0.88(8)	4.17 ± 0.44 (8)	-

The ratio of AUC of ramelteon and M-II on Day 1 to those on Day 7 was approximately 0.97-1.25, suggesting that ramelteon does not accumulated in serum after multiple doses given once daily.

	8mg			16mg		
	Day 1 AUC (ng·hr/mL)	Day 7 AUC (ng·hr/mL)	Ratio of AUC (Day 7 /Day 1)	Day 1 AUC (ng·hr/mL)	Day 7 AUC (ng·hr/mL)	Ratio of AUC (Day 7 /Day 1)
TAK-375	2.3389	2.6420	1.1564	4.2294	6.0761	1.2500
M-II	234.7870	229.0650	0.9731	339.4778	380.3872	1.1188

The ratio of Cmax of ramelteon and M-II on Day 1 to those on Day 7 was similar to those of AUC, suggesting that ramelteon does not accumulated in serum after multiple dose given only daily.

	8mg			16mg		
	Day 1 C_{max} (ng/mL)	Day 7 C_{max} (ng/mL)	Ratio of C_{max} (Day 7 /Day 1)	Day 1 C_{max} (ng/mL)	Day 7 C_{max} (ng/mL)	Ratio of C_{max} (Day 7 /Day 1)
TAK-375	1.389	1.469	1.3093	1.845	2.424	1.1924
M-II	54.178	54.151	1.0933	75.580	76.604	1.0279

2.2.4.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Ramelteon PK parameters show a large variability. Comparing across the studies, the standard deviation of PK parameters were as much as 100%, making ramelteon a highly variable drug.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Ramelteon age-related differences were statistically significant. Dose adjustments based on age may be recommended, due to 2-fold increase in ramelteon exposure. M II concentrations were greater than 10-fold higher than ramelteon. No differences in urinary excretion were noted between the older and younger subjects or between men and women in this study.

Age and gender comparison: Ramelteon was administered as a single 16 mg to healthy adults and elderly subjects.

Age: Ramelteon AUC(0-inf) and Cmax were 97% and 86% higher, respectively, and T1/2 was 66% longer in older subjects (n=24, equal number of men and women; 63 - 79 years of age) compared with younger (n=24, equal number of men and women; 18-34 years of age) subjects. M II AUC, Cmax and T1/2 were 30% and 13% higher, and 33% longer, respectively, in elderly compared with younger subjects.

Observed PK parameters: Age

Analyte	Parameter (Units)	Elderly Mean (SD)[a]	Nonelderly Mean (SD)[a]	Based on Pairwise Comparison: Ratio[b] (%)	Based on Pairwise Comparison: P Value[c]
TAK-375	AUC_{0-inf} (ng•h/mL)	18.7 (19.4)	10.5 (12.8)	197.4	0.011
	C_{max} (ng/mL)	11.6 (13.8)	6.90 (7.62)	185.63	0.024
	$T_{1/2}$ (h)	2.60 (1.14)	1.57 (0.77)	-	0.004[d,e]
M-I	AUC_{0-inf} (ng•h/mL)	15.9 (5.18)	10.9 (2.30)	142.9	<0.001
	C_{max} (ng/mL)	8.69 (2.70)	6.77 (2.17)	128.32	0.008
	$T_{1/2}$ (h)	1.04 (0.28)	0.79 (0.15)	-	0.001[d]
M-II	AUC_{0-inf} (ng•h/mL)	482.6 (143.5)	375.9 (132.9)	129.9	0.009
	C_{max} (ng/mL)	124.9 (32.0)	110.2 (29.7)	113.48	0.091
	$T_{1/2}$ (h)	3.21 (0.67)	2.42 (0.57)	-	0.001[d]
M-III	AUC_{0-inf} (ng•h/mL)	7.08 (2.88)	6.43 (4.06)	121.1	0.31
	C_{max} (ng/mL)	2.72 (1.08)	2.28 (0.93)	119.4	0.12
	$T_{1/2}$ (h)	1.25 (0.35)	1.37 (0.63)	-	0.80[e]
M-IV	AUC_{0-inf} (ng•h/mL)	113.9 (36.3)	96.1 (29.0)	117.9	0.056
	C_{max} (ng/mL)	13.9 (3.58)	13.7 (3.28)	106.16	0.362[d]
	$T_{1/2}$ (h)	5.17 (1.02)	4.45 (1.21)	-	0.012[e]

[a]Arithmetic mean (standard deviation)

[b]Ratio is based on natural log transformed parameters of adjusted mean including AGE+GENDER in the model

[c]Based on ANOVA including AGE+GENDER in the model

[d]Based on ANOVA including WEIGHT+AGE+GENDER in the model

[e]The P value provided in this table is derived from the statistical analysis of λz. It is, however, reflective of the significance of any changes of $T_{1/2}$.

Gender: Ramelteon AUC(0-inf) and Cmax were 32% and 19% higher, respectively, and T1/2 was 23% longer in women compared with men; the analysis indicated that these changes were not statistically significant. There was no gender differences observed on exposure to M-II.

Observed PK parameters: Gender

Analyte	Parameter (Units)	Female Mean (SD)[a]	Male Mean (SD)[a]	Based on Pairwise Comparison: Ratio[b] (%)	Based on Pairwise Comparison: P Value[c]
TAK-375	AUC_{0-inf} (ng•h/mL)	16.6 (16.0)	12.5 (17.6)	132.3	0.28
	C_{max} (ng/mL)	9.57 (8.33)	8.93 (13.8)	119.16	0.51
	$T_{1/2}$ (h)	2.30 (1.23)	1.57 (0.92)	-	0.017[d,e]
M-I	AUC_{0-inf} (ng•h/mL)	13.9 (4.11)	13.2 (5.47)	110.1	0.24
	C_{max} (ng/mL)	7.95 (2.45)	7.51 (2.79)	107.19	0.45
	$T_{1/2}$ (h)	0.83 (0.18)	1.02 (0.29)	-	0.017[d]
M-II	AUC_{0-inf} (ng•h/mL)	453.7 (150.4)	404.8 (142.6)	113.0	0.21
	C_{max} (ng/mL)	121.1 (27.7)	114.9 (35.0)	107.75	0.31
	$T_{1/2}$ (h)	2.83 (0.81)	2.80 (0.67)	-	0.8[e]
M-III	AUC_{0-inf} (ng•h/mL)	7.35 (3.49)	5.93 (3.18)	127.2	0.21
	C_{max} (ng/mL)	2.82 (1.03)	2.15 (0.92)	132.93	0.014
	$T_{1/2}$ (h)	1.12 (0.25)	1.52 (0.62)	-	0.034[d]
M-IV	AUC_{0-inf} (ng•h/mL)	117.7 (27.0)	92.3 (35.5)	132.1	0.002
	C_{max} (ng/mL)	15.5 (2.91)	12.0 (2.93)	118.94	0.026[d]
	$T_{1/2}$ (h)	4.90 (1.20)	4.71 (1.14)	-	0.56[e]

[a]Arithmetic mean (standard deviation)

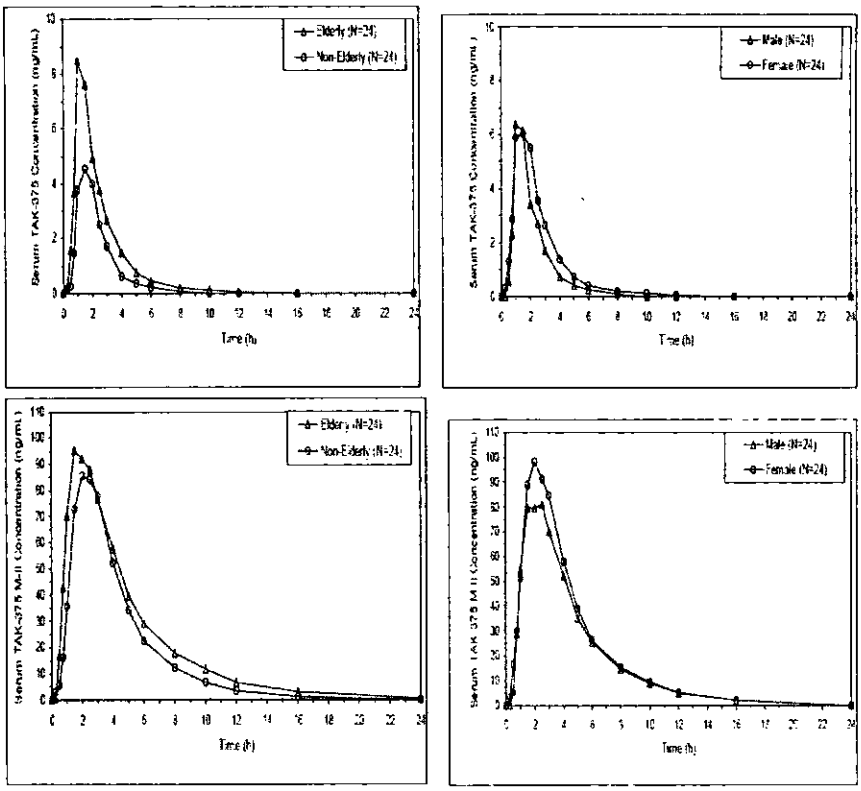
[b]Ratio is based on natural log transformed parameters of adjusted mean including AGE+GENDER in the model

[c]Based on ANOVA including AGE+GENDER in the model

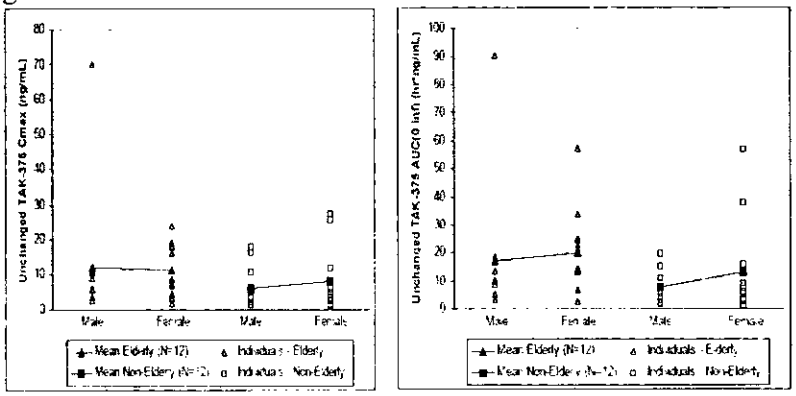
[d]Based on ANOVA including WEIGHT+AGE+GENDER in the model

[e]The P value provided in this table is derived from the statistical analysis of λz. It is, however, reflective of the significance of any changes of $T_{1/2}$.

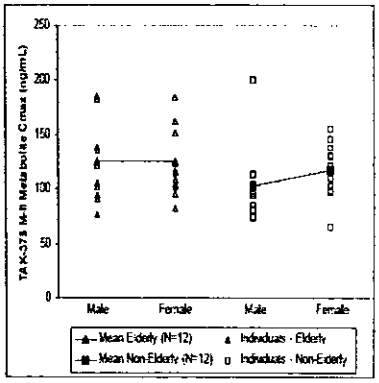
Mean serum profiles of all subjects: Ramelteon and Metabolite II

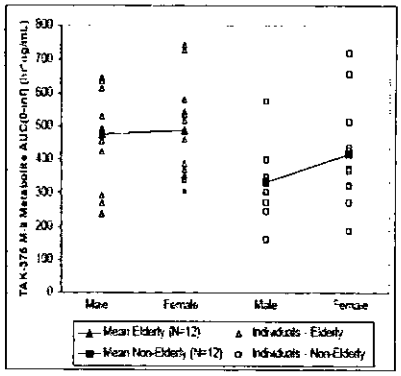


Gender by Age Comparison: Individual and means for ramelteon by age and gender:



Individual and means for M II by age and gender:





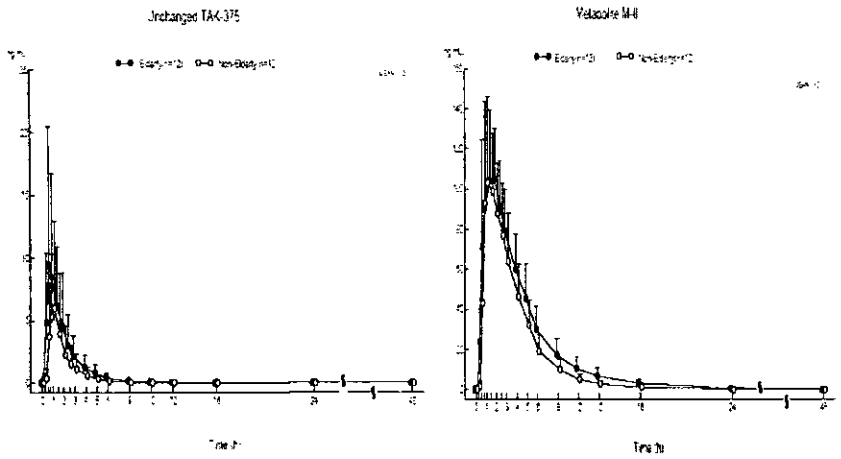
Pharmacodynamic results: No differences from Baseline or between older and younger subjects were observed for any of the pharmacodynamic parameters examined in this study; however, there appeared to be more subject- and observer-reported sedation with ramelteon than with placebo, and older subjects, particularly older men, appeared to perform slightly worse than the other groups on the 1-hour word recall test.

Age comparison : single-dose ramelteon 16 mg in Japanese men

Japanese healthy men (12 men, 20-28 years of age; 12 men, 67-75 years of age) received a single dose of ramelteon 16 mg. Ramelteon AUC(0-inf) and Cmax were approximately 85% and 31% higher, respectively, in older compared with younger men. Mean T1/2 increased 65%, and Tmax was approximately 15% longer.

Similar results were seen for the metabolites. M II AUC(0-inf) was approximately 27% higher in older compared with younger men. No differences were observed for Cmax. Mean T1/2 increased 40%, and Tmax was approximately 30% longer.

No differences in urinary excretion were noted between older and younger men, and no pharmacodynamic effects related to ramelteon administration were observed in this study. Serum profiles of ramelteon and metabolite 2, and pharmacokinetic parameters are below.



Ramelteon 16 mg PK parameters:

PK Parameter	Mean (S.D.)	
	Elderly subjects N=12	Non-elderly subjects N=12
AUC_{∞} (ng·hr/mL)	16.42 (15.72)	10.25 (10.39)
AUC_{0-24} (ng·hr/mL)	16.42 (15.72)	10.23 (10.36)
C_{max} (ng/mL)	3.81 (10.50)	7.46 (6.95)
T_{max} (hr)	1.04 (0.46)	0.90 (0.46)
MRT (hr)	2.19 (0.51)	1.69 (0.30)
VRT (hr^2)	2.97 (0.79)	1.32 (0.53)
AUC_{∞} (ng·hr/mL)	15.48 (15.71)	10.29 (10.41)
MRT_{∞} (hr)	2.26 (0.31)	1.77 (0.29)
k_e (hr^{-1})	0.45 (0.09)	0.74 (0.15)
$t_{1/2}$ (hr)	1.59 (0.32)	0.96 (0.19)
Cl_s/F (L/hr)	1804.10 (1658.85)	3197.56 (2758.65)
Vd_{ss}/F (L)	4059.51 (5309.84)	4295.54 (3775.28)

M II PK parameters:

PK Parameter	Mean (S.D.)	
	Elderly subjects N=12	Non-elderly subjects N=12
AUC_{0-24} (ng·hr/mL)	518.48 (164.58)	401.46 (121.08)
AUC_{0-24} (ng·hr/mL)	511.18 (156.74)	400.96 (119.73)
C_{max} (ng/mL)	125.86 (32.30)	128.16 (27.39)
T_{max} (hr)	1.30 (0.49)	1.13 (0.41)
MRT (hr)	4.61 (0.67)	3.44 (0.56)
VRT (hr^2)	17.00 (7.68)	8.17 (2.75)
AUC_{∞} (ng·hr/mL)	514.59 (162.79)	400.73 (120.01)
MRT_{∞} (hr)	4.54 (0.60)	3.46 (0.54)
k_e (hr^{-1})	0.22 (0.05)	0.32 (0.07)
$t_{1/2}$ (hr)	3.29 (0.75)	2.30 (0.53)

2.3.2 Is dosage adjustments needed in the following populations?

2.3.2.1 Elderly

Ramelteon exposure in elderly subjects were approximately 90 to 100 % more than that of the adults. Dosage adjustment may be required.

Ramelteon AUC and Cmax in elderly were 97 % and 86% higher, respectively, than younger adults. Metabolite II AUC and Cmax in elderly were 30 % and 14 % higher, respectively, than younger adults.

There is an evidence that ½ adult dose will be efficacious in elderly. Combined with the fact that exposures are almost doubled and clinical efficacy, it is recommended that elderly should receive ½ of the adult dosing.

2.3.2.2 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

The Applicant requested a deferral of the requirement to conduct insomnia studies in the pediatric population. The Agency has agreed to the Applicant's request (June 22, 2004); the rationale was that since ramelteon has a novel mechanism of action, the Agency would prefer to have postmarketing safety data from adults before commencing studies in pediatric population.

2.3.2.3 Gender and race differences in ramelteon exposure

Gender analysis indicated that there are no significant ramelteon exposure differences due to gender. No dose adjustment is required. Comparison between Japanese and Caucasian population revealed that there is no race differences in ramelteon exposure.

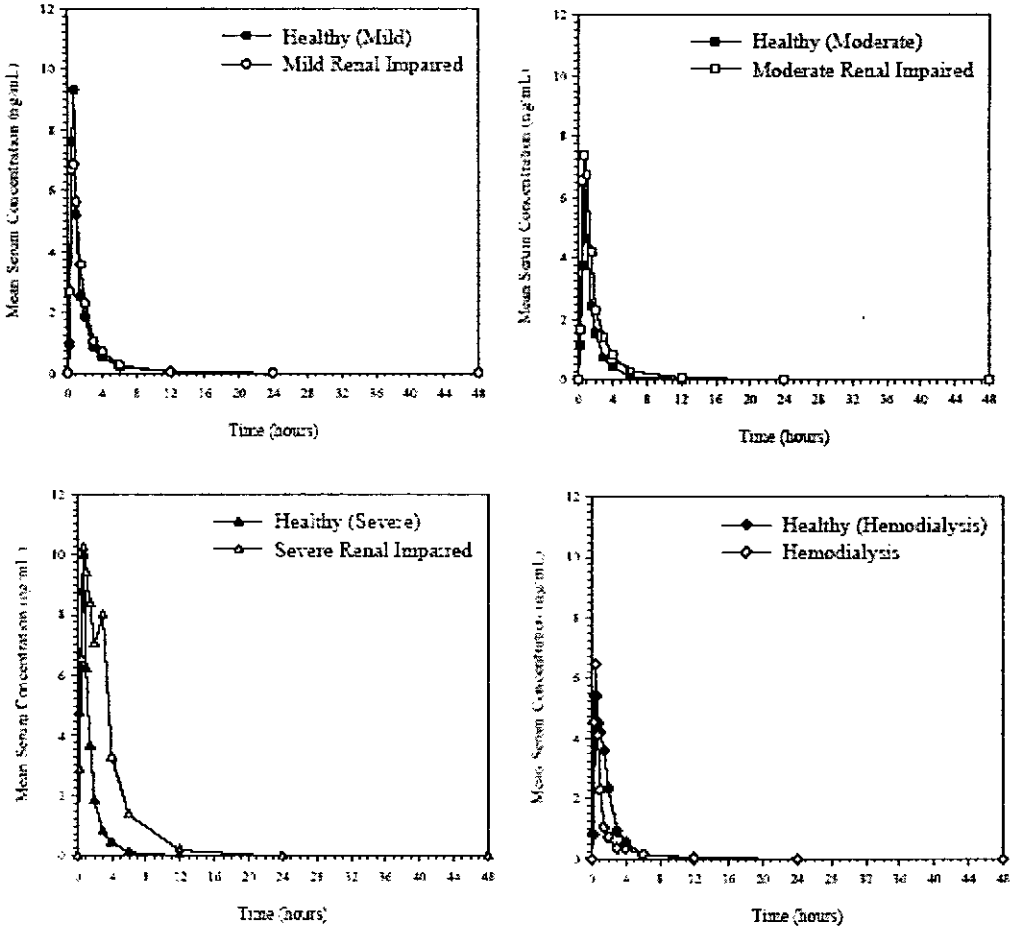
2.3.2.4 Renal impairment

The pharmacokinetic parameters showed a large variability. The major elimination route for ramelteon is via hepatic metabolism. Ramelteon and M-II are not eliminated by the kidneys, and the dialysis extraction coefficient indicated that system ramelteon exposure will not be reduced by dialysis. No clinically meaningful differences were noted in exposures to ramelteon and M-II between subjects with mild, moderate, or severe renal impairment, and healthy subjects. There was no apparent correlation between renal function, as determined by creatinine clearance and ramelteon Cmax and AUC values. No dose adjustment may be recommended when ramelteon is administered to patients with renal impairment including those who require chronic hemodialysis.

The pharmacokinetic profile of single and multiple doses of ramelteon was obtained in subjects with varying degrees of renal impairment (mild n=8, moderate n=5, and severe impairment n=7 [not including subjects who require chronic hemodialysis], and subjects who require chronic hemodialysis n=8) based on creatinine clearance, and healthy subjects matched on the basis of race, gender, age (±10 years), and weight (±30%). Subjects received a single dose of ramelteon 16 mg on Day 1 followed by a 2-day washout on Days 2 and 3. Subjects received ramelteon 16 mg QD on Days 4 through 8.

Day 1

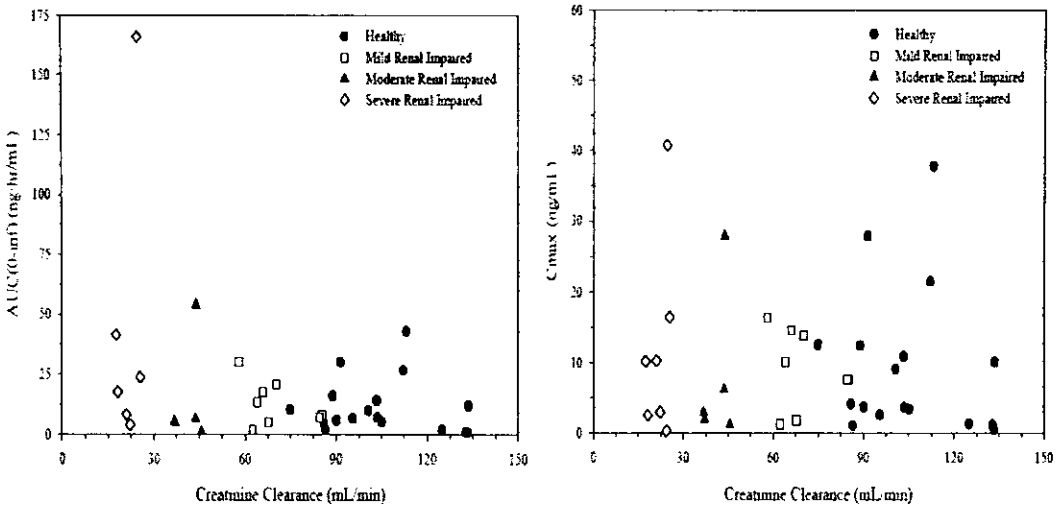
Mean Serum Concentration of Ramelteon on Day 1:



Comparison Results for Ramelteon on Day 1:

Comparison	Parameter	Least Squares Means		Mean Ratio (%) (100*T/R)	90% CI of Ratio (%)	P-value
		Healthy (a) (R)	Renal Impaired (b) (T)			
Mild to Healthy (N=8 vs 8)	Cmax (ng/mL)	6.76	6.81	100.71	(37.32, 271.77)	0.9900
	AUC(0-tlqc) (ng*hr/mL)	8.98	9.20	102.43	(42.60, 246.30)	0.9616
	AUC(0-inf) (ng*hr/mL)	9.31	9.61	103.14	(43.63, 243.83)	0.9496
Moderate to Healthy (N=8 per group)	Cmax (ng/mL)	5.53	4.15	75.07	(21.41, 263.23)	0.6821
	AUC(0-tlqc) (ng*hr/mL)	6.95	5.80	83.46	(20.40, 341.39)	0.8174
	AUC(0-inf) (ng*hr/mL)	7.12	6.08	85.31	(21.73, 334.84)	0.8343
Severe to Healthy (N=7 per group)	Cmax (ng/mL)	4.35	5.79	133.09	(29.81, 594.25)	0.7394
	AUC(0-tlqc) (ng*hr/mL)	5.20	13.5	259.64	(54.15, 1244.85)	0.2993
	AUC(0-inf) (ng*hr/mL) (c)	5.47	21.2	387.71	(88.07, 1706.80)	0.1288
Hemodialysis to Healthy (N=9 vs 4)	Cmax (ng/mL)	4.48	5.56	124.25	(39.51, 390.80)	0.7400
	AUC(0-tlqc) (ng*hr/mL)	7.02	4.87	69.33	(21.49, 223.66)	0.5836
	AUC(0-inf) (ng*hr/mL) (d)	7.42	4.54	61.01	(16.15, 230.44)	0.5127

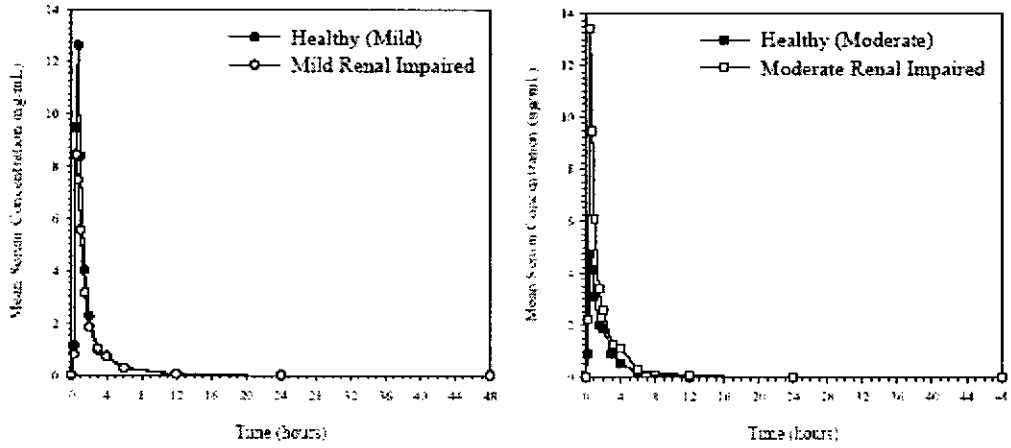
Ramelteon AUC(0-inf) and Cmax versus Creatinine Clearance on Day 1:

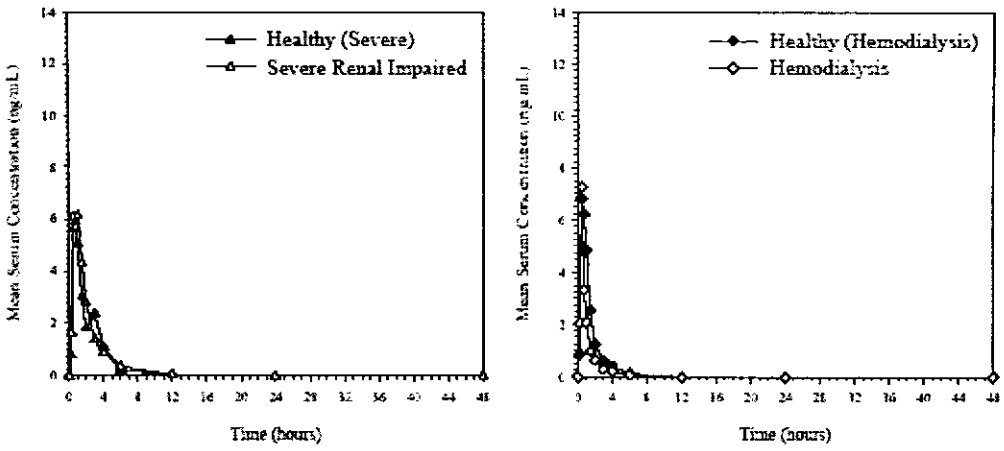


There was no discernable correlation between renal function (CLCr) and ramelteon Cmax or AUC(0-inf) values in subjects with mild, moderate, or severe renal impairment and their healthy matched controls. As the CLCr decreased, neither ramelteon Cmax nor AUC values had an observable increase on Day 1. However, 1 individual with severe renal impairment had a markedly higher AUC(0-inf) value on Day 1. Generally there was no consistent change in individual subject M-II Cmax and AUC values on Day 1 with increasing severity in renal impairment.

Day 8:

Mean Serum Concentration of Ramelteon on Day 8:



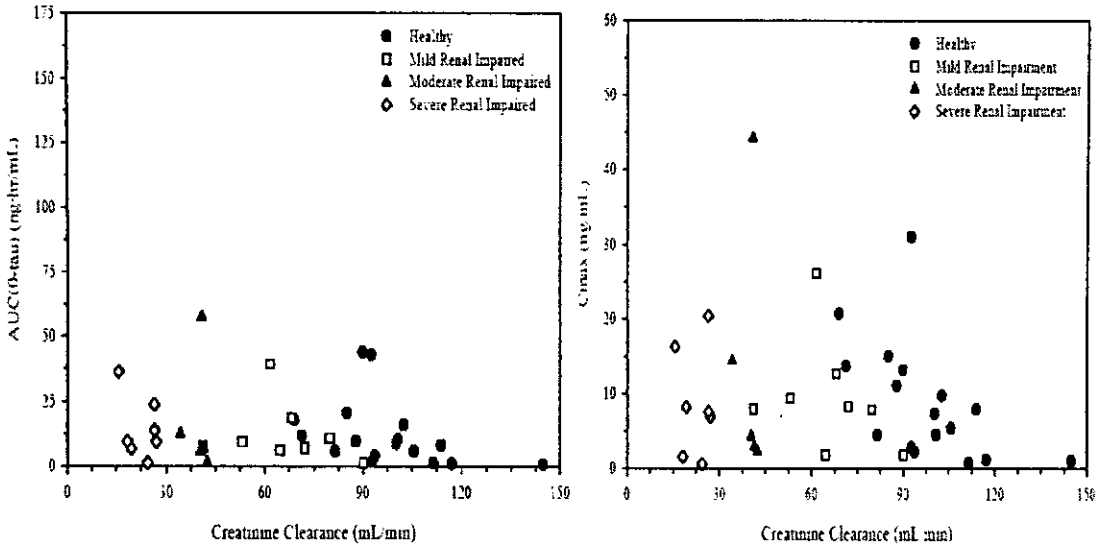


Comparison Results for Ramelteon on Day 8:

Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Renal Impaired (b) (T)	Mean Ratio (%) (100*T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy (N=8 vs 5)	Cmax (ng/mL)	11.0	7.05	64.23	(27.36, 150.79)	0.3716
	AUC(0-τ) (ng·hr/mL)	12.1	8.94	73.63	(30.30, 178.95)	0.5484
Moderate to Healthy (N=5 per group)	Cmax (ng/mL)	4.40	7.25	164.80	(44.99, 603.73)	0.4947
	AUC(0-τ) (ng·hr/mL)	6.57	8.46	128.83	(33.80, 491.02)	0.7338
Severe to Healthy (N=7 per group)	Cmax (ng/mL)	4.53	5.47	120.96	(36.95, 395.98)	0.7798
	AUC(0-τ) (ng·hr/mL)	5.63	10.2	180.61	(53.30, 612.03)	0.4049
Hemodialysis to Healthy (N=8 vs 4)	Cmax (ng/mL)	5.93	3.87	65.34	(17.08, 250.05)	0.5782
	AUC(0-τ) (ng·hr/mL)	7.07	3.47	49.04	(14.38, 167.21)	0.3172

Generally there was no consistent change in individual subject ramelteon AUC and Cmax values on Day 8 with increasing severity in renal impairment. Ramelteon Cmax and AUC(0-τ) were not markedly different in subjects with mild to severe renal impairment compared to their healthy controls following multiple dosing. Individual subject CLr values for ramelteon were low and did not appear different in the subjects with renal impairment compared to the healthy controls. In the group of hemodialysis subjects, ramelteon Cmax and AUC(0-τ) values were 35% and 51% lower, respectively, compared to their healthy controls on Day 8.

Relationship Between ramelteon AUC(0-τ) and Cmax, and Renal Function on Day 8:



There was no discernable correlation between CLcr and ramelteon Cmax or AUC(0-τ) values in subjects with mild, moderate, or severe renal impairment and their healthy controls as observed on Day 8.

Generally there was no consistent change in individual subject M-II Cmax and AUC values on Day 8 with increasing severity in renal impairment.

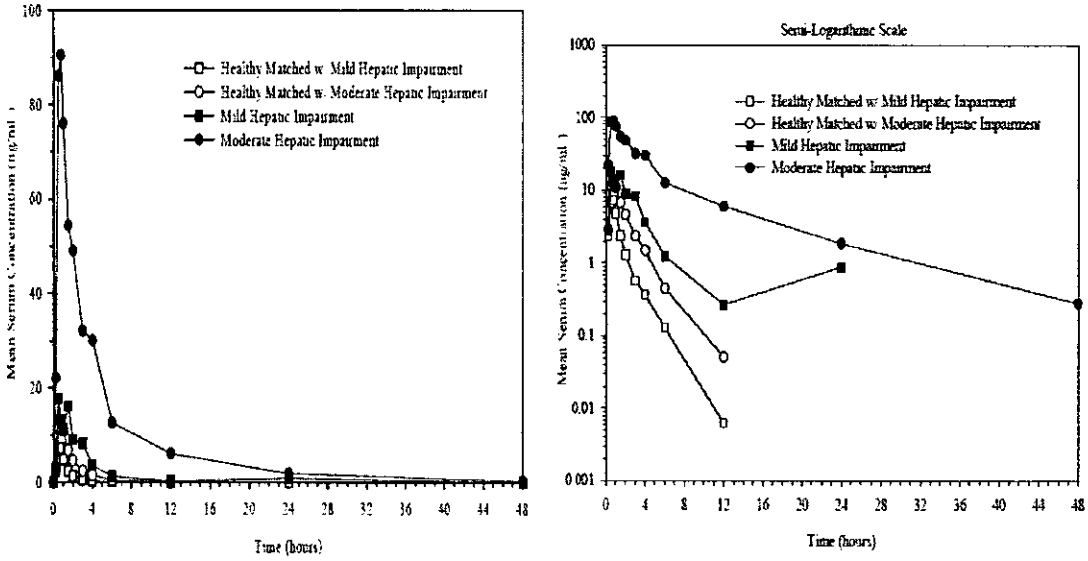
2.3.2.5 Hepatic impairment

Single and multiple dose administration of 16 mg ramelteon resulted in significant increases in exposure to ramelteon in subjects with mild hepatic impairment (3.5 to 3.6-fold higher AUCs) and moderate hepatic impairment (8.0 to 10.7-fold higher AUCs) relative to their corresponding healthy matched controls. Exposure to major metabolite M-II was only marginally increased in mildly and moderately hepatically impaired subjects relative to the respective healthy matched controls. Severe hepatic impairment group was not studied. Despite the increases in AUC, ramelteon AEs were not any different from that of the control groups. Ramelteon should be contraindicated in hepatically impaired group. (See Appendix for Study review)

The pharmacokinetic profile of single and multiple doses of ramelteon was obtained in subjects (12 subjects with mild hepatic impairment matched with 12 healthy subjects, and 12 subjects with moderate hepatic impairment matched with 12 healthy subjects) with mild and moderate hepatic impairment according to the Child-Pugh classification system. Subjects received a single dose of ramelteon 16 mg on Day 1 followed by a 2-day washout on Days 2 and 3. Subjects received ramelteon 16 mg QD on Days 4 through 8. All doses were administered in the morning under fasting conditions.

Day 1:

Ramelteon: Mean Serum Concentration of Ramelteon on Day 1:

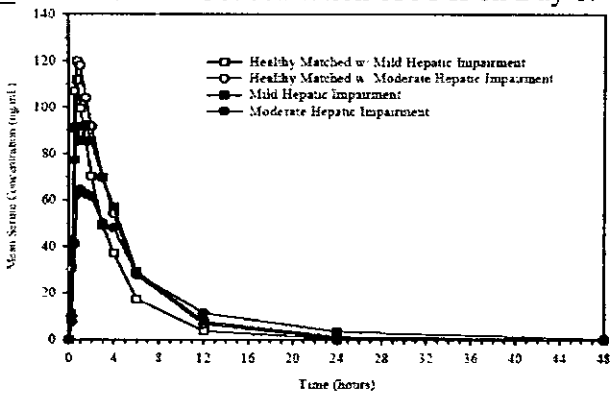


Comparison Results for Ramelteon on Day 1:

		Least Squares Means				
Comparison	Parameter	Healthy (a) (R)	Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	4.43	21.1	476.14	(186.83, 1213.44)	0.0090
	AUC(0-tlqc) (ng·hr/mL)	5.02	28.6	569.58	(212.79, 1524.60)	0.0061
	AUC(0-inf) (ng·hr/mL)	6.99	24.2	346.34	(138.07, 868.78)	0.0306
Moderate to Healthy	Cmax (ng/mL)	10.7	60.9	570.38	(237.99, 1367.02)	0.0024
	AUC(0-tlqc) (ng·hr/mL)	13.2	130	987.61	(357.89, 2725.32)	0.0008
	AUC(0-inf) (ng·hr/mL)	13.6	109	797.40	(295.02, 2155.30)	0.0017

There was significantly higher exposure (8-fold increase in AUC for moderately impaired) of ramelteon in mildly and moderately hepatically impaired subjects compared to the healthy matched controls on Day 1. The moderately impaired group had larger increases in exposure relative to the healthy matched controls. Urinary excretion of ramelteon was minimal and did not appear different in the hepatically impaired subjects compared to the matched healthy control groups.

Metabolite II: Mean Serum Concentration of M-II on Day 1:



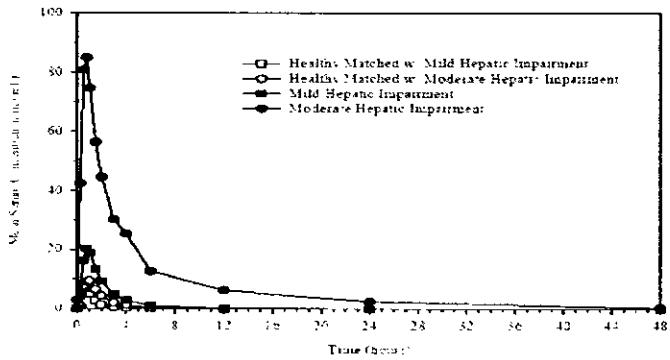
Comparison Results for M-II on Day 1:

		Least Squares Means				
Comparison	Parameter	Healthy (a) (R)	Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	120	124	103.40	(80.55, 132.74)	0.8202
	AUC(0-tlqc) (ng-hr/mL)	364	497	136.47	(104.15, 178.83)	0.0609
	AUC(0-inf) (ng-hr/mL)	371	509	137.12	(104.47, 179.97)	0.0588
Moderate to Healthy	Cmax (ng/mL)	142	73.5	51.73	(35.65, 75.06)	0.0060
	AUC(0-tlqc) (ng-hr/mL)	501	498	99.56	(76.23, 130.03)	0.9775
	AUC(0-inf) (ng-hr/mL)	508	515	101.43	(77.57, 132.61)	0.9286

There was 36 to 37% higher exposure of M-II in mildly hepatically impaired subjects relative to the healthy matched controls on Day 1, but the increase was not statistically significant. The moderately impaired group had only 1% higher exposure to M-II relative to the healthy matched controls. Urinary excretion of M-II was low and did not appear to be different in the hepatically impaired subjects as compared to the corresponding healthy matched controls.

Day 8:

Ramelteon: Mean Serum Concentration of Ramelteon on Day 8:



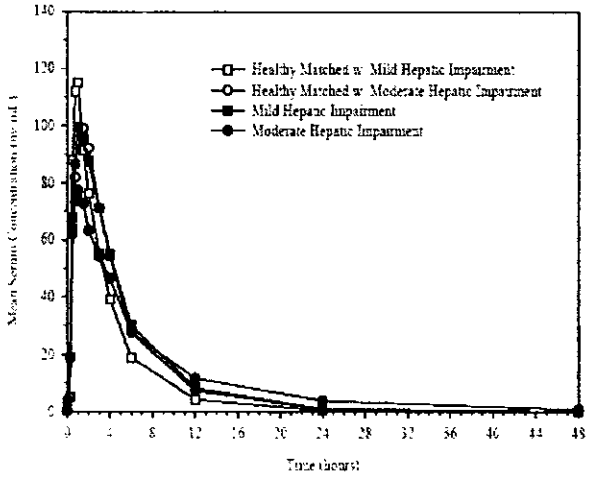
Comparison Results for Ramelteon on Day 8 :

Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	5.20	12.8	246.17	(88.19, 687.15)	0.1460
	AUC(0-τ) (ng·hr/mL)	5.79	20.7	358.16	(121.91, 1052.28)	0.0543
Moderate to Healthy	Cmax (ng/mL)	7.37	61.7	837.03	(379.45, 1846.43)	0.0001
	AUC(0-τ) (ng·hr/mL)	11.7	125	1067.25	(415.62, 2740.53)	0.0003

Similar to the Day 1 results, there was higher exposure of ramelteon in mildly and moderately hepatically impaired subjects relative to the healthy matched controls on Day 8. The moderately impaired group had larger increases in exposure (10-fold increase in AUC) relative to the healthy matched controls, which in part was attributed to 3 moderately impaired subjects who had at least 4-fold higher ramelteon exposure than the other 9 moderately impaired subjects.

The 3 moderately impaired subjects with the highest ramelteon exposure had the highest Child-Pugh scores (9 versus 7 or 8 in other moderate impaired subjects). Urinary excretion of ramelteon was low in both the hepatically impaired subject groups and their matched healthy controls.

Metabolite II : Mean Serum Concentration of M-II on Day 8 :



Comparison Results for M-II on Day 8 :

Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	124	117	94.28	(75.15, 118.27)	0.6598
	AUC(0-τ) (ng·hr/mL)	401	519	129.32	(100.03, 167.19)	0.0996
Moderate to Healthy	Cmax (ng/mL)	107	80.5	75.48	(58.04, 98.17)	0.0796
	AUC(0-τ) (ng·hr/mL)	483	496	102.73	(79.82, 132.22)	0.8560

Similar to the Day 1 results, there was marginally (29%) higher exposure to M-II in mildly hepatically impaired subjects compared to the healthy matched controls on Day 8. Moderately impaired subjects had only a 3% increase in exposure to M-II compared to the healthy matched controls.

Urinary excretion of M-II was minimal and did not appear different in the hepatically impaired subjects compared to the matched healthy matched controls.

Safety profile from this study : Adverse event table for hepatic study

	Treatment Group			
System Organ Class Preferred Term (a)	Healthy Matched to Mild Hepatic Impairment N=12	Mild Hepatic Impairment N=12	Healthy Matched to Moderate Hepatic Impairment N=12	Moderate Hepatic Impairment N=12
Gastrointestinal Disorders				
Constipation	1 (8.3)	0 (0)	0 (0)	0 (0)
Flatulence	1 (8.3)	0 (0)	0 (0)	0 (0)
Loose Stools	0 (0)	0 (0)	0 (0)	1 (8.3)
Nausea	0 (0)	0 (0)	0 (0)	2 (16.7)
General Disorders and Administration Site Conditions				
Lethargy	1 (8.3)	0 (0)	1 (8.3)	3 (25.0)
Musculoskeletal and Connective Tissue Disorders				
Myalgia	1 (8.3)	0 (0)	0 (0)	0 (0)
Nervous Systems Disorders				
Dizziness	1 (8.3)	1 (8.3)	0 (0)	1 (8.3)
Headache NOS	2 (16.7)	2 (16.7)	2 (16.7)	2 (16.7)
Somnolence	6 (50.0)	8 (66.7)	9 (75.0)	7 (58.3)
Respiratory, Thoracic, and Mediastinal Disorders				
Nasal Congestion	0 (0)	1 (8.3)	0 (0)	1 (8.3)
Pharyngitis	0 (0)	1 (8.3)	0 (0)	1 (8.3)

Despite the increases in AUC, ramelteon AEs were not any different from that of the control groups.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Ramelteon undergo extensive hepatic metabolism. CYP 1A2, 2C9, and 3A4 enzymes are involved in metabolic process. Therefore, any concomitantly administered drugs or substances which will inhibit above enzymes will likely to increase ramelteon concentrations in vivo and either used with caution or should be contraindicated. Pharmacokinetics of [ ] has not been studied in smokers, as smoking induces CYP1A2 activity.

2.4.2 Drug-Drug Interactions

2.4.2.1 Effects of Other Drugs on Ramelteon

Ramelteon metabolism is significantly hindered by CYP1A2 inhibition. CYP3A4, 2C9, and 2D6 inhibitors will suppress the metabolism of ramelteon

1A2 inhibition: Fluvoxamine study (See Appendix for study review)

Ramelteon concomitant administration with fluvoxamine should be contraindicated. These results confirm the substantial role of the CYP1A2 pathway in the metabolism of ramelteon, and are consistent with the results of the in vitro findings.

The effect of fluvoxamine, a potent CYP1A2 inhibitor, was studied on the single-dose pharmacokinetics of ramelteon and its metabolites. Subjects were randomized to receive either (1) nothing on Days 1 through 3, then a single dose of ramelteon 16 mg on Day 4 or (2) fluvoxamine 100 mg BID on Days 1 through 4 plus a single dose of ramelteon 16 mg on Day 4. Subjects crossed over to the opposite treatment after a 14-day washout.

Ramelteon AUC(0-inf) and Cmax increased approximately 190-fold and 70-fold, respectively, when ramelteon was administered with fluvoxamine compared with ramelteon administered alone. Ramelteon CL/F was reduced 99.6% (18.73 L/hr with concomitant administration of ramelteon and fluvoxamine vs 4368.26 L/hr when ramelteon was administered alone). Ramelteon Tmax was delayed by approximately 16 minutes with concomitant administration of fluvoxamine and ramelteon compared with administration of ramelteon alone; the difference was statistically significant. Ramelteon T1/2 increased approximately 3-fold (4.12 hours compared with 1.34 hours) when ramelteon was administered with fluvoxamine.

M-II AUC(0-inf) increased 31% and Cmax decreased 60% when ramelteon was administered with fluvoxamine. M-II Tmax was delayed by approximately 47 minutes when ramelteon was administered with fluvoxamine compared with ramelteon administered alone; the difference was statistically significant. M-II T1/2 increased 165% (6.35 hours compared with 2.40 hours) when ramelteon was administered with fluvoxamine.

Effect of Fluvoxamine on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Fluvoxamine	Alone	+ Fluvoxamine	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	7.98 (8.96)	1021.19 (393.24)	5.076	963.722	18987.20 (14078.54, 25607.33)
Cmax (ng/mL)	6.23 (6.85)	281.24 (95.19)	3.860	278.375	7211.72 (5262.06, 9883.75)
Tmax (hr) (b)	0.75 (0.50, 2.00)	0.98 (0.73, 2.00)	N/A	N/A	N/A
T1/2 (hr)	1.34 (0.69)	4.12 (1.15)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	336.514 (85.320)	448.683 (147.262)	333.853	436.128	130.63 (114.85, 148.58)
Cmax (ng/mL)	117.464 (42.687)	48.864 (23.801)	116.046	46.119	39.74 (33.57, 47.04)
Tmax (hr) (b)	0.75 (0.50, 2.00)	1.00 (0.50, 2.50)	N/A	N/A	N/A
T1/2 (hr)	2.40 (0.57)	6.35 (1.86)	N/A	N/A	N/A

3A4 inhibition: Ketoconazole study

Both ramelteon and M II metabolism was hindered by 3A4 inhibition. These results confirm the role of the CYP3A4 pathway in the metabolism of ramelteon.

The effect of ketoconazole, a CYP3A4 inhibitor, was studied on the single-dose pharmacokinetics of ramelteon and its metabolites. Subjects were randomized to receive either (1) nothing on Days 1 through 3, then a single dose of ramelteon 16 mg on Day 4 or (2) ketoconazole 200 mg BID on Days 1 through 4 plus a single dose of ramelteon 16 mg on Day 4. Subjects crossed over to the opposite treatment after a 14-day washout.

Ramelteon AUC(0-inf) and Cmax were 84% and 36% higher, respectively, when ramelteon was administered with ketoconazole compared with ramelteon administered alone. There was a significant difference in ramelteon Tmax between ramelteon administered alone (mean = 0.69 hours) and ramelteon administered with ketoconazole (mean = 1.02 hours). The T1/2 of ramelteon increased 31% when ramelteon and ketoconazole were administered concomitantly.

Serum M-II AUC(0-inf) and Cmax were 93% and 23% higher, respectively, when ramelteon was administered with ketoconazole compared with ramelteon administered alone. There was a significant difference in M-II Tmax between ramelteon administered alone (mean = 0.90 hours) and ramelteon administered with ketoconazole (mean = 1.44 hours). The T1/2 of M-II increased 52% when ramelteon and ketoconazole were administered concomitantly.

Effect of Ketoconazole on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Ketoconazole	Alone	+ Ketoconazole	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	11.682 (12.245)	21.306 (23.684)	6.89	12.71	184.37 (157.25, 216.16)
Cmax (ng/mL)	9.802 (9.851)	14.166 (16.189)	5.75	7.81	135.82 (109.91, 167.85)
Tmax (hr) (b)	0.74 (0.47, 1.00)	0.78 (0.48, 2.50)	N/A	N/A	N/A
T1/2 (hr)	1.37 (0.48)	1.80 (1.19)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	406.618 (127.944)	790.194 (276.589)	381.98	738.47	193.33 (182.42, 204.89)
Cmax (ng/mL)	134.646 (39.644)	163.935 (43.922)	127.30	156.71	123.10 (113.06, 134.04)
Tmax (hr) (b)	0.78 (0.25, 1.53)	1.50 (0.50, 2.55)	N/A	N/A	N/A
T1/2 (hr)	2.65 (0.63)	4.02 (0.69)	N/A	N/A	N/A

N=26.
N/A indicates not applicable.
(a) Ratio of the LS means = (ramelteon + ketoconazole/ramelteon alone) × 100.
(b) Tmax = median (minimum, maximum).

2C9 inhibition: Fluconazole study

Both ramelteon and M II metabolism was hindered by 2C9 inhibition. These results confirm the role of the CYP2C9 pathway in the metabolism of ramelteon.

Dose adjustment may be recommended when ramelteon is administered with fluconazole or other drugs that inhibit CYP2C9.

The effect of fluconazole, a CYP2C9 inhibitor, was studied on the single-dose pharmacokinetics of ramelteon and its metabolites. Subjects were randomized to receive either (1) nothing on Days 1 through 3, then a single dose of ramelteon 16 mg on Day 4, or (2) fluconazole 400 mg QD on Day 1, fluconazole 200 mg QD on Days 2 through 4 plus a single dose of ramelteon 16 mg on Day 4. Subjects crossed over to the opposite treatment after a 14-day washout.

Ramelteon AUC(0-inf) and Cmax increased 152% and 144%, respectively, when ramelteon was administered with fluconazole compared with ramelteon administered alone. Ramelteon T1/2 increased by approximately 33% when ramelteon was administered with fluconazole.

M-II AUC(0-inf) and Cmax increased 199% and 55%, respectively, when ramelteon was administered with fluconazole. M-II Tmax was delayed by approximately 19 minutes when ramelteon was administered with fluconazole compared with ramelteon administered alone, and the difference was statistically significant. M-II T1/2 was approximately 94% longer when ramelteon was administered with fluconazole.

Effect of Fluconazole on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Fluconazole	Alone	+ Fluconazole	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	8.42 (9.19)	19.88 (17.24)	5.05	12.72	252.01 (215.02,295.37)
Cmax (ng/mL)	7.56 (8.44)	16.86 (14.24)	4.33	10.57	243.86 (192.93, 308.23)
Tmax (hr) (b)	0.75 (0.48, 1.50)	0.64 (0.27, 2.50)	N/A	N/A	N/A
T1/2 (hr)	1.10 (0.32)	1.46 (0.55)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	369.87 (114.48)	1058.02 (174.59)	350.39	1046.99	298.81 (274.98, 324.70)
Cmax (ng/mL)	124.21 (27.23)	191.54 (39.88)	122.70	190.16	154.98 (142.79, 168.21)
Tmax (hr) (b)	0.88 (0.50,1.53)	1.00 (0.75,2.52)	N/A	N/A	N/A
T1/2 (hr)	2.41 (0.71)	4.67 (0.76)	N/A	N/A	N/A

2C19 inhibition: Omeprazole study

Both ramelteon and M II metabolism was not hindered by 2C19 inhibition. Rather, omeprazole acted as an inducer. No dose adjustment is recommended when ramelteon is administered with omeprazole or other drugs that inhibit CYP2C19.

The effect of omeprazole, a CYP2C19 inhibitor, was studied on the multiple-dose pharmacokinetics of ramelteon and its metabolites, (and the effects of ramelteon on the multiple-dose pharmacokinetics of omeprazole, a CYP2C19 substrate – see Section 2.4.2.2.). Subjects were randomized to 1 of 6 sequences and received either ramelteon 16 mg alone, omeprazole 40 mg alone, or concomitant administration of ramelteon 16 mg and omeprazole 40 mg dosed QD in three 7-day treatments. Dosing was separated by 5 days of washout.

Omeprazole is both a substrate and an inhibitor of CYP2C19; however, it also acted as a CYP1A2 inducer at the high doses used in this study. Concomitant administration of ramelteon and omeprazole decreased peak and total exposure to ramelteon by approximately 30%. M-II Cmax and AUC increased by 16% and 29%, respectively.

Effect of Omeprazole on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Omeprazole	Alone	+ Omeprazole	Ratio (90% CI) (a)
Ramelteon					
AUC(0-τ) (ng·hr·mL)	6.43 (7.46)	4.07 (4.31)	3.90	2.62	67.31 (59.87, 75.68)
Cmax (ng/mL)	5.32 (8.02)	3.39 (3.91)	2.84	2.06	72.65 (58.54, 90.16)
Tmax (hr) (b)	0.75 (0.50, 2.0)	0.75 (0.50, 2.5)	N/A	N/A	N/A
T1/2 (hr)	1.20 (0.58)	1.15 (0.64)	N/A	N/A	N/A
M-II					
AUC(0-τ) (ng·hr/mL)	337 (116)	435 (135)	322	416	129.19 (122.97, 135.71)
Cmax (ng/mL)	112 (36.9)	130 (39.0)	106	123	116.08 (106.93, 126.00)
Tmax (hr) (b)	1.00 (0.50, 3.00)	1.00 (0.50, 2.50)	N/A	N/A	N/A
T1/2 (hr)	2.14 (0.59)	3.16 (1.05)	N/A	N/A	N/A

2D6, 2C9, 2C19, and 3A4 inhibition : Fluoxetine study

These results indicate that fluoxetine inhibits the metabolism of ramelteon and M-II modestly. Dose adjustment may not be needed if ramelteon is administered with fluoxetine, a 2D6 inhibitor.

The effect of fluoxetine, an SSRI, was studied on the single-dose pharmacokinetics of ramelteon and its metabolites [45]. Fluoxetine is both a substrate and a potent inhibitor of CYP2D6 activity; however, it also inhibits CYP2C9, CYP2C19, and CYP3A4.

Subjects received a single dose of ramelteon 16 mg on Day 1, followed by fluoxetine 40 mg QD on Days 3 through 12, then single doses of fluoxetine 40 mg and ramelteon 16 mg on Day 13.

Ramelteon Cmax and AUC increased 40% to 50%, respectively, after a single ramelteon 16 mg dose was administered with fluoxetine. Cmax and AUC values for M-II increased 17% and 52%, respectively, in the presence of fluoxetine.

Effect of Fluoxetine on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		Geometric Mean		
	Ramelteon		Ramelteon		
	Alone	+ Fluoxetine	Alone	+ Fluoxetine	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	8.47 (9.52)	11.1 (13.0)	4.66	7.00	150.09 (127.11, 177.21)
Cmax (ng/mL)	7.44 (9.29)	10.0 (14.7)	3.85	5.38	139.81 (117.92, 165.77)
Tmax (hr) (b)	0.75 (0.50, 1.50)	0.75 (0.50, 2.50)	N/A	N/A	N/A
T1/2 (hr)	1.21 (0.60)	1.29 (0.63)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	344 (117)	511 (134)	326	495	151.69 (142.55, 161.42)
Cmax (ng/mL)	121 (34.6)	142 (39.1)	116	136	116.73 (108.24, 125.90)
Tmax (hr) (b)	0.82 (0.50, 1.55)	1.00 (0.67, 5.00)	N/A	N/A	N/A
T1/2 (hr)	2.39 (0.54)	2.96 (0.60)	N/A	N/A	N/A

CYP (3A4) induction: Rifampin study

Remelteon metabolism was considerably accelerated with rifampin co-administration. Dosage adjustment should be considered or contraindication is needed due to uncertainty in dosage adjustment scheme.

The effect of rifampin, a potent CYP enzyme inducer, was studied on the single-dose pharmacokinetics of ramelteon and its metabolites. Subjects received a single dose of ramelteon 32 mg on Day 1, nothing on Day 2, rifampin 600 mg QD on Days 3 through 12, and single doses of ramelteon 32 mg and rifampin 600 mg on Day 13.

Peak and total serum exposures to ramelteon decreased by approximately 80%. M-II exposure decreased by approximately 90% after multiple-dose administration of rifampin.

Effect of Rifampin on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		Geometric Mean		
	Ramelteon		Ramelteon		
	Alone	+ Rifampin	Alone	− Rifampin	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	25.3 (25.43)	5.30 (6.77)	15.1	2.85	18.91 (15.12, 23.66)
Cmax (ng/mL)	18.2 (16.3)	4.09 (5.66)	11.4	2.04	17.90 (14.17, 22.60)
Tmax (hr) (b)	0.75 (0.50, 1.50)	0.75 (0.50, 2.00)	N/A	N/A	N/A
T1/2 (hr)	1.13 (0.33)	0.92 (0.26)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	794 (241)	91.4 (45.2)	760	82.7	10.88 (9.82, 12.06)
Cmax (ng/mL)	230 (58.2)	47.5 (24.5)	223	42.3	18.99 (16.86, 21.38)
Tmax (hr) (b)	1.00 (0.50, 3.03)	0.75(0.50, 2.00)	N/A	N/A	N/A
T1/2 (hr)	3.26 (0.71)	0.98 (0.16)	N/A	N/A	N/A

2D6 Substrate : Dextromethorphan study

No changes in ramelteon profiles were observed, as predicted by in vitro metabolism.

The effect of dextromethorphan was studied on the single-dose pharmacokinetics of ramelteon and its metabolites, and the effects of ramelteon on the single-dose pharmacokinetics of dextromethorphan, a CYP2D6 substrate, its major metabolite, dextrorphan, and 2 of its minor metabolites, 3-hydroxymorphinan and 3-methoxymorphinan. Subjects were randomized to 1 of 6 sequences and received single doses of either ramelteon 32 mg alone, dextromethorphan 30 mg alone, or concomitant administration of ramelteon 32 mg and dextromethorphan 30 mg in three 1-day treatments. Dosing was separated by 7 days of washout.

Exposure to ramelteon and its metabolites in serum was similar when ramelteon was administered alone or with dextromethorphan.

Effect of Dextromethorphan on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Dextromethorphan	Alone	+ Dextromethorphan	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng hr/mL)	14.1 (13.9)	14.3 (16.7)	9.63	9.82	101.96 (89.63, 115.98)
Cmax (ng/mL)	9.86 (8.91)	11.0 (13.1)	7.00	7.46	106.61 (90.12, 126.11)
Tmax (hr) (b)	0.75 (0.25, 4.00)	0.75 (0.25, 1.03)	N/A	N/A	N/A
T1/2 (hr)	1.07 (0.32)	1.16 (0.56)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng-hr/mL)	754 (284)	767 (289)	714	726	101.59 (98.39, 104.90)
Cmax (ng/mL)	226 (76.2)	215 (54.7)	214	208	97.18 (90.39, 104.48)
Tmax (hr) (b)	1.00 (0.75, 4.00)	1.00 (0.25, 1.52)	N/A	N/A	N/A
T1/2 (hr)	2.11 (0.71)	2.20 (0.71)	N/A	N/A	N/A

1A2 Substrate : Theophylline study

Ramelteon Cmax and AUC(0-τ) increased approximately 35% to 40%, respectively, with theophylline co-administration compared with administration of ramelteon alone. No dose adjustment is needed.

The effect of theophylline was studied on the multiple-dose pharmacokinetics of ramelteon and its metabolites, and the effects of ramelteon on the multiple-dose pharmacokinetics of theophylline, a CYP1A2 substrate with a narrow therapeutic range. Subjects were randomized to 1 of 4 sequences and received either (1) ramelteon 32 mg alone, then concomitant administration of ramelteon 32 mg and theophylline 300 mg, (2)

theophylline 300 mg alone, then concomitant administration of ramelteon 32 mg and theophylline 300 mg, (3) concomitant administration of ramelteon 32 mg and theophylline 300 mg, then ramelteon 32 mg alone, or (4) concomitant administration of ramelteon 32 mg and theophylline 300 mg, then theophylline 300 mg alone. All study drugs were dosed QD in two 10-day treatments. Dosing was separated by 5 days of washout.

Concomitant administration of theophylline and ramelteon resulted in approximately 35% to 40% increases in ramelteon Cmax and AUC(0-τ), respectively, compared with administration of ramelteon alone.

M-II AUC(0-τ) values increased by 12% when ramelteon was administered with theophylline compared with when ramelteon was administered alone. There were no differences in M-II values for Cmax, Tmax or T1/2 when ramelteon was administered alone or in combination with theophylline.

Effect of Theophylline on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Theophylline	Alone	+ Theophylline	Ratio (90% CI) (a)
Ramelteon					
AUC(0-τ) (ng·hr/mL)	30.0 (21.1)	42.2 (30.0)	22.2	31.1	140.48 (123.26, 160.12)
Cmax (ng/mL)	26.3 (19.6)	34.5 (26.0)	18.4	25.0	135.41 (107.61, 170.39)
Tmax (hr) (b)	0.52 (0.50, 1.50)	0.54 (0.50, 1.12)	N/A	N/A	N/A
T1/2 (hr)	1.41 (0.60)	1.53 (0.61)	N/A	N/A	N/A
M-II					
AUC(0-τ) (ng·hr/mL)	722 (227)	802 (197)	693	774	111.70 (99.55, 125.35)
Cmax (ng/mL)	220 (49.9)	225 (66.3)	214	216	100.89 (89.08, 114.26)
Tmax (hr) (b)	0.76 (0.75, 1.50)	1.00 (0.50, 2.05)	N/A	N/A	N/A
T1/2 (hr)	2.42 (0.83)	2.48 (0.74)	N/A	N/A	N/A

Alcohol interaction study

Ramelteon Cmax and AUC(0-inf) increased by 43% and 47%, respectively, with alcohol administration. No differences were noted in exposure to M-II after concomitant administration of ramelteon and ethanol.

Interaction between ramelteon and alcohol was studied in the Study 028 (PK only) and Studies 028 and 043 (PD only). Subjects in both studies were randomized to 1 of 4 sequences; each sequence consisted of four, 1-day treatments, which included (1) ramelteon 32 mg plus placebo ethanol, (2) ethanol 0.6 g/kg plus placebo ramelteon, (3) ramelteon 32 mg plus ethanol 0.6 g/kg, and (4) placebo ramelteon plus placebo

ramelteon. Each treatment was separated by 6 days of washout. Pharmacodynamics (psychomotor performance and memory, and alertness) were assessed in both studies.

In Study 028, ramelteon Cmax and AUC(0-inf) increased by 43% and 47%, respectively, with alcohol administration; these increases in exposure were not statistically significant. No differences were noted in exposure to M-II after concomitant administration of ramelteon and ethanol.

Effect of Ethanol on the Pharmacokinetics of Ramelteon and M-II :

	Arithmetic Mean (±SD)		LS Mean		
	Ramelteon		Ramelteon		
	Alone	+ Ethanol	Alone	+ Ethanol	Ratio (90% CI) (a)
Ramelteon					
AUC(0-inf) (ng·hr/mL)	18.7 (20.1)	25.1 (25.1)	11.8	17.4	146.79 (104.23, 206.73)
Cmax (ng/mL)	9.65 (10.0)	13.7 (18.1)	5.81	8.30	142.85 (93.53, 218.19)
Tmax (hr) (b)	2.00 (0.50, 3.00)	2.00 (0.50, 4.00)	N/A	N/A	N/A
T1/2 (hr)	1.17 (0.28)	1.18 (0.44)	N/A	N/A	N/A
M-II					
AUC(0-inf) (ng·hr/mL)	725 (263)	777 (213)	682	748	109.53 (101.27, 118.46)
Cmax (ng/mL)	155 (26.5)	157 (28.8)	153	154	100.69 (92.19, 109.97)
Tmax (hr) (b)	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	N/A	N/A	N/A
T1/2 (hr)	2.53 (0.88)	2.72 (0.90)	N/A	N/A	N/A

In all studies, the pharmacodynamic interaction was observed in some of the PD parameters. Because alcohol by itself impairs performance and the intended effect of ramelteon is to promote sleep, and because concomitant administration of ramelteon and ethanol in the 2 ethanol interaction studies had some additive effects on performance, as assessed on measures of psychomotor function, patients should be advised to use caution if they take ramelteon in combination with alcohol.

2.4.2.2 Effects of Ramelteon on other drugs

Ramelteon as a 2C19 inhibor: Omeprazole study

Ramelteon did not hinder omeprazole metabolism, suggesting that it is not a CYP2C19 inhibitor.

The effect of ramelteon on the multiple-dose pharmacokinetics of omeprazole, was studied, a CYP2C19 substrate. No differences were noted in the peak and total exposures to omeprazole after administration of omeprazole alone or with ramelteon.

Effect of Ramelteon on the Pharmacokinetics of Omeprazole :

	Arithmetic Mean (±SD)		LS Mean		
	Omeprazole		Omeprazole		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Omeprazole					
AUC(0-inf) (ng·hr/mL)	3987 (2363)	3893 (2475)	3464	3318	95.80 (91.82, 99.94)
Cmax (ng/mL)	1514 (572)	1524 (671)	1425	1396	97.96 (87.89, 109.18)
Tmax (hr) (b)	2.00 (0.75, 4.00)	2.00 (1.00, 5.00)	N/A	N/A	N/A
T1/2 (hr)	1.36 (0.55)	1.33 (0.55)	N/A	N/A	N/A

2D6 Substrate: Dextromethorphan study

No changes were observed. Ramelteon is not an inhibitor of the CYP2D6 isozyme. Additionally, ramelteon had no inhibitory effect on the CYP3A4-mediated metabolism of dextrorphan to 3-hydroxymorphinan, which confirmed the results of the midazolam study.

The effect of ramelteon was studied on the single-dose pharmacokinetics of dextromethorphan, a CYP2D6 substrate, its major metabolite, dextrorphan, and 2 of its minor metabolites, 3-hydroxymorphinan and 3-methoxymorphinan, and the effects of dextromethorphan on the single-dose pharmacokinetics of ramelteon and its metabolites.

No differences were noted in the plasma pharmacokinetics of total dextromethorphan, total 3-hydroxymorphinan, and total dextrorphan after administration of dextromethorphan alone and with ramelteon. Plasma concentration of 3-methoxymorphinan was too low to derive its pharmacokinetic parameters.

Effect of Ramelteon on the Pharmacokinetics of Dextromethorphan, 3-hydroxymorphinan, and Dextrorphan :

	Arithmetic Mean (±SD)		LS Mean		
	Dextromethorphan		Dextromethorphan		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Dextromethorphan					
AUC(0-inf) (ng·hr/mL)	18.3 (31.2)	18.9 (27.6)	10.1	11.1	109.99 (100.99, 119.79)
Cmax (ng/mL)	3.48 (6.38)	3.19 (5.09)	1.35	1.42	104.67 (95.39, 114.86)
Tmax (hr) (b)	2.50 (1.50, 4.00)	2.50 (1.50, 8.00)	N/A	N/A	N/A
T1/2 (hr)	7.90 (8.50)	7.71 (6.86)	N/A	N/A	N/A
3-Hydroxymorphinan					
AUC(0-inf) (ng·hr/mL)	1181 (352)	1230 (336)	1134	1167	102.86 (100.35, 105.44)
Cmax (ng/mL)	158 (64.7)	157 (61.4)	132	131	99.30 (95.00, 103.78)
Tmax (hr) (b)	2.50 (1.50, 3.05)	2.75 (1.50, 4.05)	N/A	N/A	N/A
T1/2 (hr)	4.68 (1.49)	4.64 (1.30)	N/A	N/A	N/A
Dextrorphan					
AUC(0-inf) (ng·hr/mL)	2101 (515)	2137 (470)	2047	2088	102.01 (99.47, 104.61)
Cmax (ng/mL)	406 (170)	393 (162)	328	323	98.57 (93.20, 104.26)
Tmax (hr) (b)	1.50 (0.75, 2.50)	1.50 (1.00, 3.02)	N/A	N/A	N/A
T1/2 (hr)	5.39 (5.63)	5.12 (4.14)	N/A	N/A	N/A

1A2 Substrate: Theophylline study

Ramelteon did not hinder 1A2 activity.

The effect of ramelteon was studied on the multiple-dose pharmacokinetics of theophylline, a CYP1A2 substrate with a narrow therapeutic range, and the effects of theophylline on the multiple-dose pharmacokinetics of ramelteon and its metabolites.

The pharmacokinetics of plasma theophylline administered alone or with ramelteon were similar.

Effect of Ramelteon on the Pharmacokinetics of Theophylline :

	Arithmetic Mean (±SD)		LS Mean		
	Theophylline		Theophylline		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Theophylline					
AUC(0-τ) (ng·hr/mL)	130681 (58024)	131730 (58422)	118980	121449	102.08 (98.30,105.99)
Cmax (ng/mL)	8125 (2924)	7962 (2691)	7600	7515	98.89 (93.97, 104.06)
Tmax (hr) (b)	4.00 (3.00, 6.00)	4.00 (2.00, 8.12)	N/A	N/A	N/A
T1/2 (hr)	9.97 (3.22)	10.3 (3.57)	N/A	N/A	N/A

3A4 Substrate: Midazolam study

Ramelteon is neither an inhibitor nor an inducer of the CYP3A4 isozyme. Therefore, no dose adjustment will be necessary when ramelteon is administered with midazolam or other CYP3A4 substrates.

The effect of multiple doses of ramelteon was studied on the pharmacokinetics of midazolam, a CYP3A4 substrate, and its major metabolite, 1-hydroxymidazolam. All subjects received a single dose of midazolam 10 mg on Day 1, then 9 days of ramelteon administration alone (32 mg QD on Days 4 through 12), followed by single doses of ramelteon 32 mg and midazolam 10 mg on Day 13. Ramelteon and midazolam dosing was separated by 2 days of washout on Days 2 and 3.

There were no differences in the pharmacokinetics of plasma midazolam and 1-hydroxymidazolam when midazolam was administered alone or after multiple doses of ramelteon.

Effect of Ramelteon on the Pharmacokinetics of Midazolam and 1-Hydroxymidazolam :

	Arithmetic Mean (±SD)		Geometric Mean		
	Midazolam		Midazolam		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Midazolam					
AUC(0-inf) (ng·hr/mL)	139 (75.0)	129 (59.7)	126	119	94.62 (86.45, 103.56)
Cmax (ng/mL)	51.4 (35.5)	44.8 (19.0)	45.3	41.8	92.26 (82.51, 103.17)
Tmax (hr) (b)	0.50 (0.25, 1.02)	0.50 (0.25, 1.00)	N/A	N/A	N/A
T1/2 (hr)	5.21 (1.71)	5.22 (1.88)	N/A	N/A	N/A
1-Hydroxymidazolam					
AUC(0-inf) (ng·hr/mL)	58.0 (20.2)	57.1 (19.6)	55.2	54.1	97.91 (89.35, 107.29)
Cmax (ng/mL)	24.5 (10.9)	23.0 (9.64)	22.4	21.2	94.53 (81.34, 109.87)
Tmax (hr) (b)	0.50 (0.25, 1.02)	0.50 (0.50, 1.00)	N/A	N/A	N/A
T1/2 (hr)	5.55 (2.46)	5.57 (2.40)	N/A	N/A	N/A

1A2 and 2C9 Substrates: Warfarin study

Ramelteon is neither an inhibitor nor an inducer of the CYP1A2 or CYP2C9 isozymes, and no dose adjustment will be necessary when ramelteon is administered with warfarin.

The effect of multiple doses of ramelteon was studied on the steady-state pharmacokinetics of warfarin, a drug with a narrow therapeutic range. The effects of ramelteon on both the R-enantiomer of warfarin, a CYP1A2 substrate, and the pharmacologically active S-enantiomer, a CYP2C9 substrate, were analyzed.
A secondary objective of the study was to evaluate the pharmacodynamic effects of multiple doses of ramelteon on PT and INR. Twenty-four subjects enrolled and 22 subjects completed the study. All subjects were dosed as follows: a single initial, loading dose of warfarin (men 8 mg; women 6 mg) on Day -7; a single dose of warfarin (men 4 mg; women 3 mg) on Day -6; a QD warfarin dose, titrated from 1 up to 15 mg on Days -5 to -1, to achieve stable PT values within the target range of 1.2 to 1.7 times higher than pretreatment PT; the stable warfarin dose on Day 0; and the stable warfarin dose with ramelteon 16 mg QD on Days 1 to 7.

Overall exposures to R-warfarin and S-warfarin in plasma were similar after administration of warfarin alone or with ramelteon. No statistically significant differences were found in PT or INR values between warfarin administered alone (Day 0) and warfarin administered with ramelteon (Day 7) at both 15 minutes predose and 12 hours postdose, or after adjusting for predose levels.

Effect of Ramelteon on the Pharmacokinetics of Warfarin :

	Arithmetic Mean (±SD)		Geometric Mean		
	Warfarin		Warfarin		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
R-Warfarin					
DN AUC(0-24) (ng·hr/mL)	4021 (1170)	3881 (845)	3871	3798	98.10 (93.30, 103.14)
DN Cmax (ng/mL)	247 (67.3)	232 (45.3)	238	228	95.59 (90.63,100.81)
Tmax (hr) (b)	1.50 (0.50, 4.00)	1.50 (0.25, 4.00)	N/A	N/A	N/A
T1/2 (hr)	N/A	N/A	N/A	N/A	N/A
S-Warfarin					
DN AUC(0-24) (ng·hr/mL)	2987 (1493)	2722 (1042)	2731	2569	94.06 (89.39, 98.97)
DN Cmax (ng/mL)	199 (78.9)	182 (58.8)	188	174	92.85 (88.52,97.39)
Tmax (hr) (b)	0.75 (0.50, 3.00)	0.75 (0.50, 4.00)	N/A	N/A	N/A
T1/2 (hr)	N/A	N/A	N/A	N/A	N/A

P-glycoprotein Substrates: Digoxin study

The results indicated that ramelteon did not interact with a P-gp substrate. Additionally, ramelteon may not affect P-glycoprotein transport.

The effect of multiple doses of ramelteon was studied on the pharmacokinetics of digoxin, a P-glycoprotein substrate with a narrow therapeutic range. Subjects were randomized to receive either digoxin plus ramelteon 16 mg or digoxin alone on Days 1 through 12. Subjects crossed over to the opposite treatment after a 14-day washout. Digoxin was dosed at 0.5 mg in the morning, followed by 0.25 mg 12 hours later on Day 1; on Days 2 through 12, subjects received digoxin 0.2 mg QD.

Compared with digoxin administration alone, concomitant administration of digoxin and ramelteon decreased peak and total digoxin exposure by approximately 10% and 3%, respectively.

Effect of Ramelteon 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

Few differences were noted in the urinary excretion of digoxin between the 2 treatments on Day 1 and on Day 12. Digoxin steady-state exposure was not effected by ramelteon.

The changes in digoxin Cmax are not clinically meaningful, and these results suggest that ramelteon is unlikely to interact with P-glycoprotein substrates; ramelteon may not affect P-glycoprotein transport.

Alcohol interaction

Ramelteon did not change alchohol profiles when administered concomitantly.

Effect of Ramelteon on the Pharmacokinetics of Ethanol :

	Arithmetic Mean (±SD)		LS Mean		
	Ethanol		Ethanol		
	Alone	+ Ramelteon	Alone	+ Ramelteon	Ratio (90% CI) (a)
Ethanol					
AUC(0-inf) (µg·hr/mL)	2283 (580)	2273 (690)	2189	2194	100.23 (92.69, 108.38)
Cmax (µg/mL)	652 (87.8)	630 (110)	642	626	97.40 (93.06, 101.95)
Tmax (hr) (b)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	N/A	N/A	N/A
T1/2 (hr)	1.30 (0.71)	1.27 (0.56)	N/A	N/A	N/A

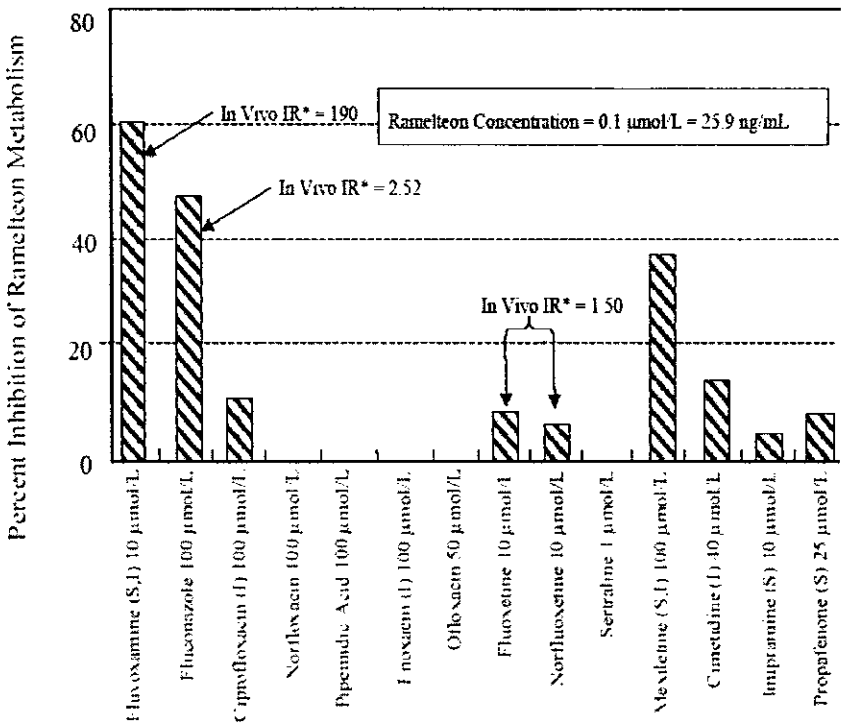
2.4.2.3 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In vitro information suggested that inhibition of 1A2 will substantially increase ramelteon in vivo concentrations.

CYP1A2 Inhibition The depletion rate constant for ramelteon was determined at concentrations of 0.1 µmol/L and 1 µmol/L. Ramelteon was incubated in pooled human hepatic microsomes with standard battery of drugs (norfloxacin, enoxacin, ofloxacin, pipemidic acid, ciprofloxacin, sertraline, fluoxetine, norfluoxetine, imipramine, cimetidine, mexiletine, or propafenone; fluvoxamine (a potent CYP1A2 inhibitor) and fluconazole (a CYP2C9 inhibitor) as controls for high and low inhibition, respectively).

Fluvoxamine and fluconazole had the most potent in vitro inhibitory effects (60.8% and 48.0%, respectively) on the metabolism of ramelteon at a ramelteon concentration of 0.1 µmol/L (25.9 ng/mL). The inhibitory effects of the other compounds on ramelteon CYP1A2-mediated metabolism were weaker than fluvoxamine or fluconazole.

Effects of Several CYP1A2 Inhibitors and Substrates, and Other Marker Drugs on the Metabolism of Ramelteon *In Vitro* :



Ramelteon concentration = 0.1 µmol/L = 25.9 ng/mL.
In Vivo IR indicates inhibitory ratio in vivo, which equals the LS mean ratio of ramelteon AUC with inhibitor, over ramelteon AUC without inhibitor; I, CYP1A2 inhibitor; S, CYP1A2 substrate.

Fluvoxamine Inhibitory Constants The inhibitory constants of fluvoxamine on the metabolism of ramelteon were studied in vitro. Pooled human hepatic microsomes from 15 donors were incubated with ramelteon at concentrations of 0.1, 0.2, and 0.5 µmol/L in the presence and absence of fluvoxamine, a potent CYP1A2 inhibitor, at concentrations of 0.03, 0.1, 0.3, and 1 µmol/L. Metabolic clearance was estimated from the depletion rate constant of ramelteon concentration vs time. The Ki of fluvoxamine was estimated from the changes in clearance vs the concentration of fluvoxamine. Fluvoxamine Ki values, in the presence of ramelteon at concentrations of 0.1, 0.2, and 0.5 µmol/L, were 0.18, 0.10, and 0.19 µmol/L, respectively (mean = 0.16 µmol/L).

Fluvoxamine Correlation The metabolic correlation (the depletion rate of ramelteon and each CYP isozyme-specific activity) between ramelteon and several CYP isozymes was studied in the presence and absence of fluvoxamine in vitro (human hepatic microsomes incubated with ramelteon in the presence and absence of fluvoxamine, a potent CYP1A2 inhibitor). Furafylline, a selective CYP1A2 inhibitor, was used as a control.

In the absence of fluvoxamine, the highest correlations were between the depletion rate of ramelteon and CYP1A2 (7-ethoxyresorufin O-dealkylation) and CYP3A (testosterone 6

β-hydroxylation) activities (r=0.853 and r=0.566, respectively). In the presence of fluvoxamine, the correlation with CYP1A2 decreased (r=0.208); however, the correlation with CYP3A increased (r=0.796). These results suggest that fluvoxamine inhibits ramelteon CYP1A2 activity but does not inhibit ramelteon CYP3A metabolism. Furafylline results were similar to the fluvoxamine results.

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes? Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Ramelteon is not an inhibitor of 1A2, 2C19, 2D6, and 3A4 enzymes. Ramelteon is not an inducer of 1A2, 2C9 and 3A4 enzymes. According to in vitro CaCo-cell study and in vivo digoxin study, ramelteon is not a P-gp inhibitor.

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The bioequivance study was not conducted between the to-be-marketed and pivotal clinical formulations.

2.5.2 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification? What data support a waiver of in vivo BE data?

The solubility of the drug substance covers over the pH range 1.1 to 7.5 at 37°C using standard aqueous buffers described in USP 26. The permeability data of the drug substance was from the mass balance study (ADME of a single 16 mg dose of [^{14}C]ramelteon) in healthy adult male subjects and in vitro Caco-2 cell intestinal permeability study. Additionally, in vitro rat portal vein metabolism study was conducted to show the ramelteon gut absorption characteristics. To bridge the formulations throughout development and to support the waiver of in vivo bioequivalence studies, the dissolution of the ramelteon drug product was tested. The dissolution conditions used were USP Apparatus II at 50 rpm and 37°C, in 900 mL of each of 3 different media (0.1 N HCl, pH 4.5 — buffer, and pH 6.8 — buffer). The Applicant's data have been forwarded to the BCS Committee, and the Committee has suggested studying ramelteon in vitro stability in simulated intestinal and gastric fluids. This recommendation has been communicated to the Applicant. Thus, the final determination will be pending further submission of data.

The Applicant submitted the following BCS classification system data in order to support a bio-waiver. See Appendix 4.2 for detailed information.

Solubility

The solubility of the drug substance was established over the pH range 1.1 to 7.5 at 37°C using standard aqueous buffers. The ramelteon drug substance is a neutral compound, having no acid or base functional groups. The solubility of ramelteon was independent of pH under the conditions of this study, being [ ] mg/mL over the pH range 1.1 to 7.5 at 37°C. These data indicate that approximately [ ] mg of ramelteon would dissolve in a — mL aqueous solution at 37°C. This amount corresponds to approximately 8- to 10-fold more than the recommended therapeutic dose of ramelteon (8 mg).

Permeability

Mass balance study:

The mass balance study was conducted (a single 16 mg dose of [^{14}C]ramelteon) in healthy adult male subjects. Urinary and fecal excretion of the administered radioactive drug was quantified. The mean radioactivity excreted in urine for the 6 subjects was 84%, indicating that at least 84% of the administered dose was absorbed through the gut. The mean radioactivity recovered in feces was 4.0% with less than 0.1% of that amount attributable to unchanged drug. These data suggest that the majority of the dose recovered in feces resulted from biliary excretion of absorbed drug as metabolites. The total percentage of ramelteon dose absorbed was approximately 88%.

In vitro permeability study:

The intestinal permeability of ramelteon was also investigated in an in vitro Caco-2 cell permeability assay using [14C]ramelteon. The Papp values for [14C]ramelteon, in the presence and absence of quinidine (a known inhibitor of P-glycoprotein), [3H]digoxin (a known substrate for P-glycoprotein), and DL-[3H]propranolol (a high permeability marker drug) were determined in both the apical-to-basolateral and basolateral-to-apical directions.

Papp for [14C]ramelteon from the apical to basolateral sides of the monolayer was similar to that from the basolateral to apical sides (27.3±5.3 x 10-6 and 28.5±2.1 x 10-6 cm/sec, respectively) and was higher than that for DL-[3H]propranolol (19.0±2.2 x 10-6 and 17.4±2.8 x 10-6 cm/sec, respectively) in either direction. Furthermore, Papp of [14C]ramelteon was not affected by quinidine.

Rat portal vein metabolism study:

Additionally, in vitro rat portal vein metabolism study was conducted to show the ramelteon gut absorption characteristics. [14C]ramelteon was injected into the jejunal loop at a dose of 1 mg/kg. Major component of radioactivity in the rat portal vein plasma

was unchanged ramelteon (96, 93, 95, and 91% of the total radioactivity at 0-0.5, 0.5-1, 1-1.5, 1.5-2 hours, respectively). The results suggested that ramelteon is stable in the intestinal tract and not metabolized in the absorption processes prior to reaching the systemic circulation.

Dissolution profiles

The dissolution of the Phase II/III 4 mg tablet (reference formulation) was compared with that of the Phase I 4 mg tablet (test formulation). The differences between these 2 formulations were minor and included [ ] used in the [ ] process and the quantity of [ ] in the tablet core. The dissolution conditions used were USP Apparatus II at 50 rpm and 37°C, in 900 mL of each of 3 different media (0.1 N HCl, pH 4.5 — buffer, and pH 6.8 — buffer). Dissolution [ ] minutes in all three media. The f2 values for 0.1N HCl, pH 4.5 — buffer, and pH 6.8 — buffer were 57.9, 69.1, and 75.2, respectively, indicating that the dissolution profiles for the Phase I and Phase II/III formulations (4 mg tablets) were similar in each of the 3 test media.

Additionally, the dissolution profiles of the 4 and 8 mg tablets for the Phase I and Phase II/III, and to-be-marketed 8 mg tablet formulations were compared using water as medium. The Phase I and Phase II/III formulations exhibited similar and rapid dissolution, with more than \ o of the label claim consistently dissolving within — minutes.

Ultimately, the Applicant proposed the following dissolution method and specification: USP apparatus II at 50 rpm, 900 mL water with a Q of \ ó in \ ninutes.

Formulation ingredient information

See *Section 2.1.1.* for list of ingredients for clinical and to-be-marketed formulations. The differences between the Phase I and Phase II/III formulations were very minor; the differences are in minimal amount of [ ] The performance between Phase I and II/III tablets are not expected.

The 8 mg commercial tablets are identical to the 8 mg Phase II/III tablets, except for the addition of [ ] Again, the performance between Phase II/III and to-be-marketed tablets are not expected.

2.5.3 What is the effect of food on the bioavailability (BA) of ramelteon tablets? What dosing recommendation should be made, if any, regarding administration of ramelteon tablets in relation to meals or meal types?

Administration with high fat breakfast results in a 30% increase in AUC, 22% decrease in Cmax, and 1 hour increase in Tmax of remelteon. Due to the delay in absorption, ramelteon should be administered without food.

The effect of food was studied on the pharmacokinetics of a single dose of ramelteon 16 mg. Food appears to increase overall exposure to unchanged ramelteon by approximately 30%. AUC(0-inf) for ramelteon was 31% higher (90% CI: [108.69%, 156.95%]) and Cmax was 22% lower (90% CI: [57.62%, 104.59%]) for fed subjects vs fasted subjects.

Median Tmax was 0.75 hours (range of 0.5 to 1.5 hours) after administration to fasted subjects, and was delayed approximately 1 hour under fed conditions. T1/2 remained essentially unchanged.

Food had little effect on M-II AUC(0-inf), but Cmax decreased 35% (90% CI: [57.16%, 74.80%]).

These data suggest that ingestion of ramelteon with food results in a slight decrease in absorption without a major decrease in the total amount of drug absorbed. Due to the delay in absorption, remelteon may be administered without food.

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Remelteon is a rapidly dissolving drug product and the proposed dissolution method and specifications reflect the findings.

Proposed dissolution method and specification are: USP apparatus II at 50 rpm, 900 mL water with a Q of \ , in \ minutes. The proposed method and specifications were justified with appropriate data.

2.6 Analytical Section

2.6.1 How are ramelteon and its metabolites measured in the serum and urine?

A validated [ ] method was used for the simultaneous quantification of unchanged total ramelteon and its metabolites M-I through M-IV in human serum and urine.

A validated [ ] method was used for the simultaneous quantification of unchanged total ramelteon and its metabolites M-I through M-IV in human serum and

urine. The Metabolite II is an active metabolite. The internal standard used for unchanged ramelteon, M-II, M-III, and M-IV was deuterated unchanged ramelteon, whereas that used for M-I was deuterated M-I. The analytes and internal standards were extracted from human serum using [redacted] was used [redacted] and the analysis was performed in the selected [redacted] The data were calculated using weighted LS linear regression. When 0.3 mL of human serum was used, the LLOQ was [redacted] ng/mL and [redacted] ng/mL for unchanged ramelteon and its metabolites, respectively, and the standard curves were linear up to [redacted] ng/mL) and [redacted] ng/mL [redacted] ng/mL) for unchanged ramelteon and its metabolites, respectively. LLOQs and concentrations used in standard curve are appropriate ranges. When 0.3 mL of human urine was used, the LLOQ was [redacted] ng/mL for unchanged ramelteon and [redacted] ng/mL for M-I through M-IV, and the standard curves were linear up to [redacted] ng/mL) and [redacted] ng/mL [redacted] ng/mL) for unchanged ramelteon and its metabolites, respectively.

2.6.1.1 What are the accuracy, precision and selectivity parameters? What is the sample stability under the conditions used in the study?

The assay validation parameters are within the usual acceptable limits. See Appendix 4.3

3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. The package insert is modified by strikeouts of the existing texts and addition of new texts.

Clinical Pharmacology

Pharmacodynamics and Mechanism of Action

[redacted]

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.2 Bio-waiver data : BCS Classification 1 support information

Solubility

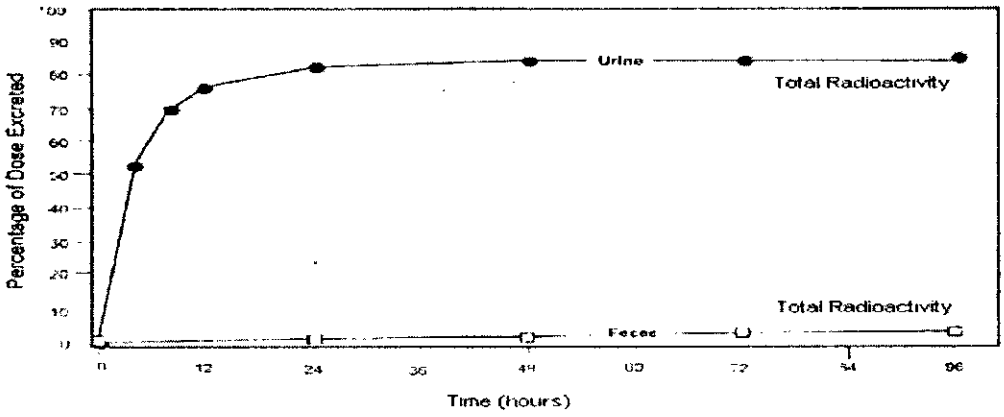
pH-Solubility Data for Ramelteon Drug Substance at 37° C

Buffer System	Repetition	pH (Initial)	pH (Final)	Solubility (mg/mL)
0 1 mol/L HCl		1.1		
buffer		3.0		
buffer		4.5		
buffer		6.8		
buffer		7.5		

Permeability

Mass balance study:

Cumulative Excretion of Total Radioactivity in Urine and Feces



Total radioactivity counts:

Time point	Percentage of administered dose						Mean	SD
	101M	102M	103M	104M	105M	106M		
0-4 h							53.28	4.79
4-8 h							16.80	1.73
8-12 h							7.05	1.04
12-24 h							5.96	1.06
24-48 h							1.81	0.52
48-72 h							0.19	0.09
72-96 h							0.01	NA
96-120 h							<0.01	NA
120-144 h							ND	NA
144-168 h							ND	NA
168-192 h							ND	NA
Urine Total							84.31	2.63
Faeces Total							3.96	1.33
Total recovery							88.27	2.32

ND = not detected, NA = not applicable

In vitro permeability study:

Table 1 Permeability of [^{14}C]TAK-375 and model drugs ([^{3}H]digoxin and DL-[^{3}H]propranolol) across Caco-2 cell monolayers

Compound	Concentration (μmol/L)	Papp ($\times 10^{-6}$ cm/sec)	
		Apical-to-basolateral	Basolateral-to-apical
[^{14}C]TAK-375	10	27.3 ± 5.3	28.5 ± 2.1
[^{14}C]TAK-375 (with 100 μmol/L quinidine)	10	27.8 ± 1.0	29.4 ± 0.5
[^{3}H]digoxin	30*	2.9 ± 0.2	16.3 ± 1.0
DL-[^{3}H]propranolol	10	19.0 ± 2.2	17.4 ± 2.8

C_0 : Initial concentration of [^{14}C]TAK-375 or model drugs

* μmol/L

Mean values ± S.D. (n=3)

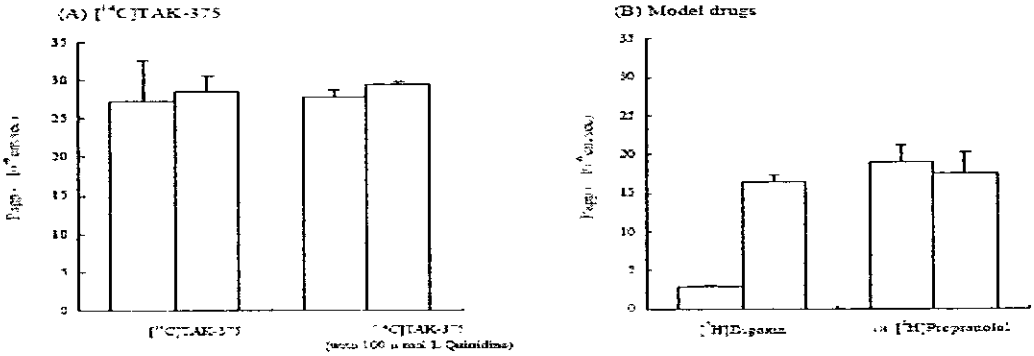


Figure 1 Permeability of [^{14}C]TAK-375 and model drugs ([^{3}H]digoxin and DL-[^{3}H]propranolol) across Caco-2 cell monolayers

Mean values ± S.D. (n=3)
Apical-to-basolateral
Basolateral-to-apical

Rat portal vein metabolism study:

Table 1 Composition of radiolabeled materials in plasma from the portal vein after administration of [^{14}C]TAK-375 into the jejunal loop of a rat

Compound	Concentration (μg TAK-375 quivalent/mL)			
	0-0.5 h	0.5-1.0 h	1.0-1.5 h	1.5-2.0 h
Total ^{14}C	4.576 (100.0)	1.955 (100.0)	0.882 (100.0)	0.444 (100.0)
TAK-375	4.393 (96.0)	1.810 (92.6)	0.833 (94.5)	0.404 (91.0)
Others	0.183 (4.0)	0.145 (7.4)	0.049 (5.5)	0.040 (9.0)

Dose: 1 mg/kg

Figures in parentheses denote % of total ^{14}C.

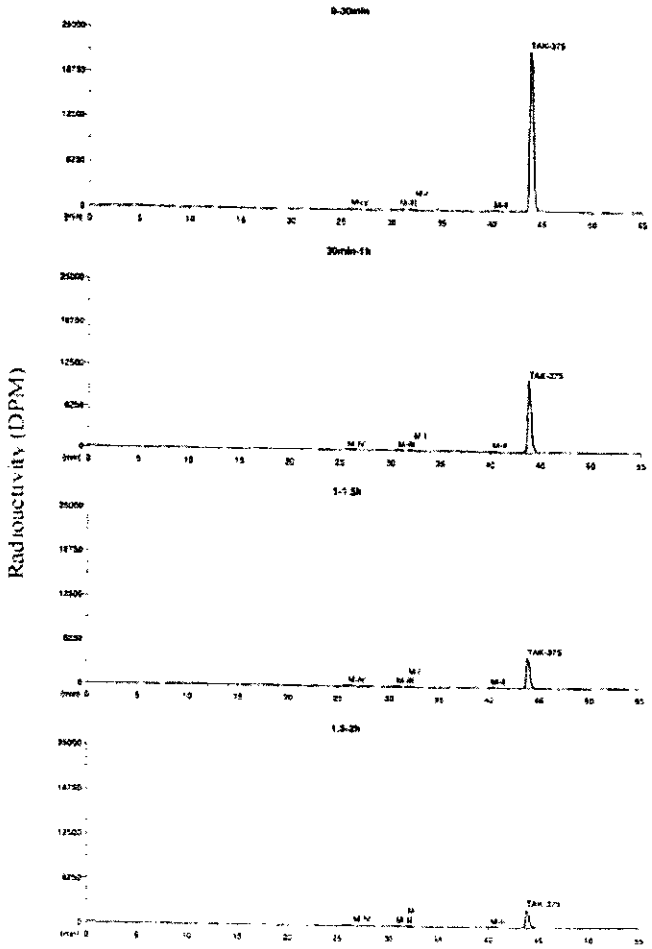


Figure 1 HPLC radiochromatogram of portal vein plasma after administration of [^{14}C]TAK-375 into the jejunal loop of a rat

Dissolution profiles

Dissolution Profiles for Phase I and Phase II/III Formulations (4 mg Tablets) in the 3 FDA-Specified Media at 37oC

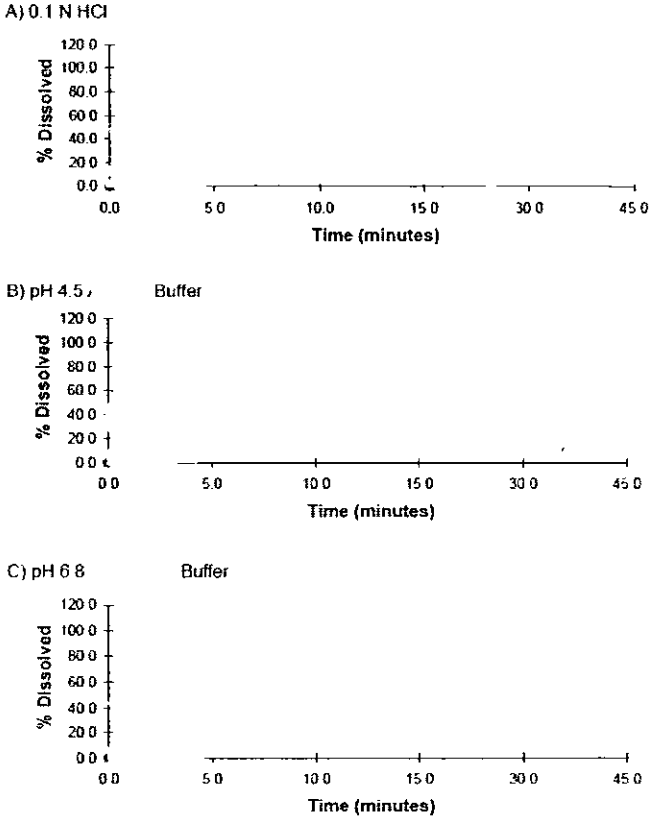
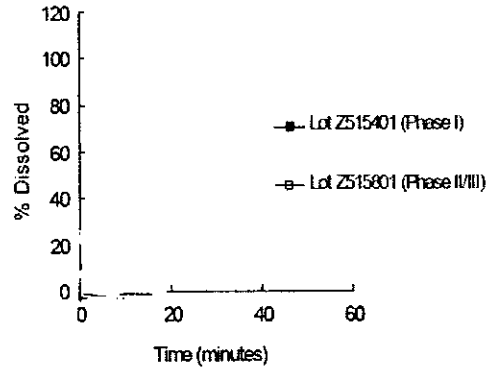


Table 4.b Summary of In Vitro Dissolution Studies in the 3 FDA-Specified Media

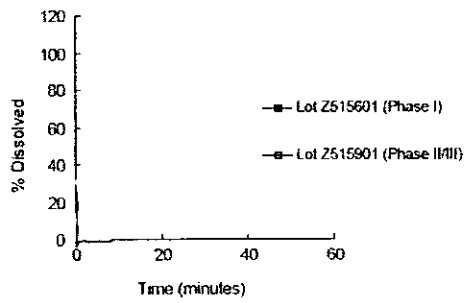
Report No.	Conditions (a)	No. of Dosage Units (a)	Dosage Form	Lot No./ Formulation	Dissolution Medium (a)	Collection Times (Min) 5	10	15	30	45
						Mean % Dissolved (Range) (%CV)				
7128-276	USP Apparatus II (paddles) at 50 rpm in 900 mL of each medium (37 C)	12/medium lot	4 mg tablets	/5158031 Phase II III (Reference)	0.1N HCl					
					pH 4.5 buffer					
					pH 6.8 buffer					
				/5158401 Phase I (Test)	0.1N HCl					
					pH 4.5 buffer					
					pH 6.8 buffer					

Dissolution Profiles for Phase I and Phase II/III Formulations in 900 mL Water at 37oC

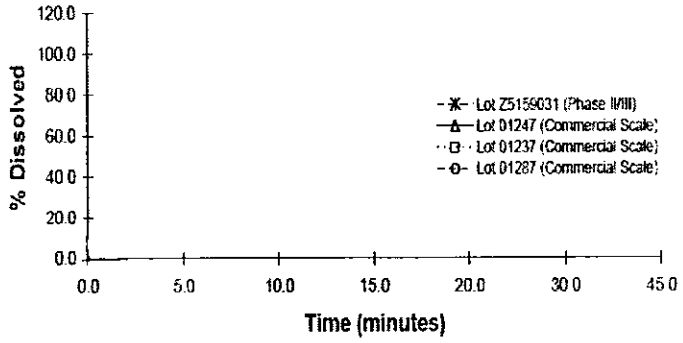
A) 4 mg Tablets



B) 8 mg Tablets



Dissolution Profiles for Phase II/III and Commercial (Pilot- and Commercial-Scale) Formulations (8 mg tablets) in 900 mL Water at 37oC



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4.3 Fluvoxamine Drug-Drug interaction and hepatic study results

4.3.1 Fluvoxamine Drug-Drug Interaction

An Open-Label, Crossover, Drug Interaction Study of the Effects of Fluvoxamine on the Pharmacokinetics of TAK-375 in Normal Healthy Male and Female Subjects

Comments: Fluvoxamine was dosed for 3 days, but, plasma levels did not reach s-s. At Day 3, the ramelteon was given.

Protocol Number: 01-01-TL-375-008

Investigator and Study Center: [redacted]

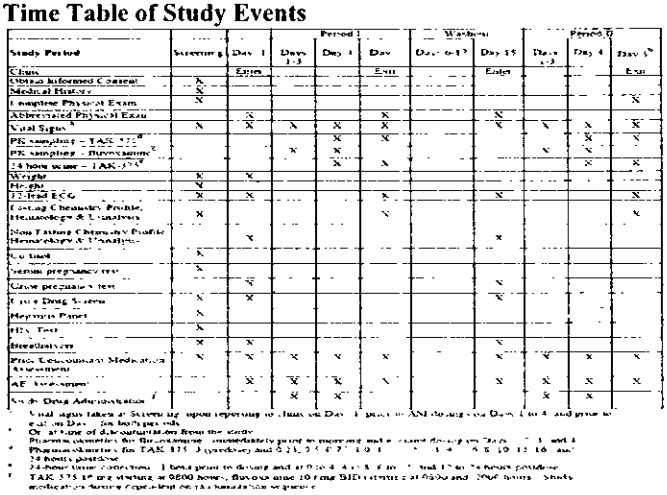
Study period (.First subject in. through .last subject out.): 09 November 2001 . 22 December 2001

Objective:

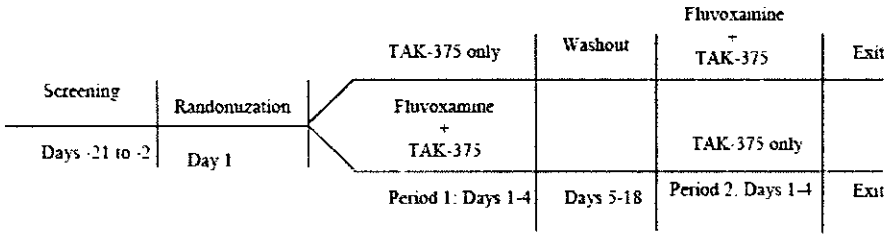
- To evaluate the effect of fluvoxamine (strong 1A2 inhibitor) on the safety and pharmacokinetics of TAK-375 in healthy adult volunteers.

Methodology: This was a single-center, open-label, crossover study in 28 healthy normal subjects (25 completed the study). The study evaluated the effects of fluvoxamine on the safety and pharmacokinetics of single doses of TAK-375 and its primary metabolites. Safety was monitored throughout the study. Subjects were admitted to the clinic on Day -1 and received either a single oral dose of TAK-375 alone on Day 4, or **fluvoxamine twice daily (BID) for 3 days**, followed by 16 mg TAK-375 plus fluvoxamine BID on Day 4. The TAK-375 and fluvoxamine AM dosing was administered starting at 0800 hours. The fluvoxamine PM dosing was administered starting at 2000 hours. On Day 4 of Periods 1 and 2, subjects fasted at least 8 hours prior to dosing and for 4 hours postdose. After a 14-day washout, subjects were then crossed over to the opposite treatment. Blood and urine samples were obtained at specified time points over a 24-hour period for pharmacokinetic evaluation. Safety was monitored throughout the study.

Time Table of Study Events



Entire Study



Selection of Doses in the Study
The 16 mg dose of TAK-375 was chosen for this study based on the following single and multiple-dose pharmacokinetic studies.

General and Dietary Restrictions

Subjects were given 3 meals and a bedtime snack each day. Total daily food intake during clinic stays contained no more than 30% to 40% calories derived from fat. Meals were served at least 30 minutes postdose in the morning with the exception of Day 4 in Periods 1 and 2. On these days, subjects fasted for a minimum of 8 hours prior to dosing and for at least 4 hours postdose. Subjects completed the meal within 30 minutes. Start/stop times, as well as all information regarding completion of meals was recorded. The same menu and meal schedule were administered uniformly for all subjects. Water was available ad libitum except for 1 hour prior to dosing through 1 hour postdose on TAK-375 dosing Day 4 for both treatment periods.

Subjects refrained from the use of all tobacco products within 90 days of study entry and during the entire study. Use of alcohol was prohibited for 48 hours before study medication administration and during the time they were confined to the clinic. Use of caffeine was prohibited for 48 hours before study medication administration and during the time subjects were confined to the clinic. Consumption of orange or orange juice, and grapefruit or grapefruit juice, within 14 days of Day-1 and during the study was not allowed. Subjects refrained from strenuous exercise throughout the entire course of the study.

Diagnosis and Main Criteria for Inclusion: Twenty-eight healthy subjects (16 men and 12 women), between the ages of 18 and 55 years, with a body mass index (BMI) <34 and without a history of insomnia were included in the study. Women of child-bearing potential had to use an acceptable method of contraception and have a negative pregnancy test result at Screening and at both check-in periods.

Test Product, Dose, and Mode of Administration; Batch Number:

Test Product	Unit Dose Form	Mode of Administration	Lot No.
TAK-375	16 mg Tablets	Oral	Z515A018

Reference Therapy, Dose and Mode of Administration, Batch Number:

Test Product	Unit Dose Form	Mode of Administration	Lot No.
Fluvoxamine	100 mg Tablets	Oral	91647

Criteria for Evaluation:

Pharmacokinetic Measures: Pharmacokinetic parameters: AUC[0-t], AUC[0-inf], Cmax, Tmax, λz, T1/2, CL/F, CLr, and Fe for urine. Pharmacokinetic samples for the analysis of serum concentrations of TAK-375 and its 4 primary metabolites (M-I through M-IV) were obtained at the following times relative to the **Day 4** dose of TAK-375 in both treatment periods: predose (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours postdose (17 sample time points). Pharmacokinetic samples for the determination of the amount of fluvoxamine in plasma were drawn separately prior to each dose (morning and evening) of fluvoxamine. Urine was collected on **Day 4** of both treatment periods at approximately 1 hour prior to dosing and at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose.

Safety measures: Safety parameters included monitoring of adverse events, vital signs, electrocardiograms (ECGs), physical exams, and clinical laboratory values.

Electrocardiograms

Scheduled 12-lead ECGs were performed at Screening, on Day -1, and on Day 5 before discharge during both Periods 1 and 2, and Day 18 of the study.

Statistical Methods:

Demographic and baseline characteristics: Descriptive statistics were used to summarize the demographic variables by treatment sequence for each age group, gender, and overall.

Prior to the estimation of the pharmacokinetic parameters, concentrations below the quantification limit (BQL) were assigned a value of 0 if they preceded quantifiable samples in the initial portion of the profile. In general, serum concentrations that were below the quantification of the assay were considered 0. However, if measurable concentrations were near the lower limit of quantification and were embedded between BQL concentrations, then these values may have been excluded at the discretion of the pharmacokineticist. (Note: for purposes of descriptive statistics of the concentration versus time data, all BQL concentrations were assigned a value of 0.)

For each analyte, a mixed effect analysis, including effects for sequence, gender, treatment, period, sequence*gender, treatment*gender, period*gender, and subject nested within sequence*gender, was performed on Tmax, λz, Cmax, AUC0-t, and AUC0-inf, where data were available. The effect for subjects nested within sequence*gender was treated as random and all other effects were considered fixed. If the P-value for the interaction terms treatment*gender and period*gender are not significant at a 5% level, then they were dropped from the model. PROC MIXED in SAS (version 8.2) was used to perform all ANOVAs.

If the interaction terms for treatment*gender or period*gender were not significant at the 5% level ($P>0.05$), then these terms were dropped from the model. Also, for Cmax, AUC(0-t), and AUC(0-inf), the 90% confidence interval (CI) for the ratio of the least square (LS) means of TAK-375 plus fluvoxamine relative to TAK-375 alone was provided.

A mixed effects analysis was performed to assess the achievement of steady state of fluvoxamine. This analysis included fixed effects for gender, day, guidetime (identifier for AM or PM sample collection), day*gender, day*guidetime, and period, and random effect for intercept were performed on the natural logs of the morning and evening predose fluvoxamine concentrations. The guidetime term identified whether the sample was a morning collection or an evening collection. If the effects for guidetime, day*guidetime interaction, or day*gender interaction were not statistically significant at the 5% level, they were dropped from the model. If the day*guidetime interaction was significant at the 5% level, the steady-state analysis was performed at each level of guidetime, namely, at AM and PM collections.

Bioanalytical Method Used in Protocol 01-01-TL-375-008 Sample Analyses

Laboratory	Matrix	Bioanalytical Method No.	Analyte(s) Measured	Assay Range (ng/mL)
	Serum		TAK - 375	
			M . I	
			M . II	
			M . III	
			M . IV	
	Urine		TAK - 375	
			M . I	
			M . II	
			M . III	
			M . IV	
	Plasma		Fluvoxamine	

Safety: Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized by system organ class and preferred term for different treatment groups and gender-by-treatment. Descriptive statistics were used to summarize clinical laboratory data and vital signs. Changes from baseline were also summarized for vital signs. Laboratory data were also summarized using shift tables. Incidence of electrocardiogram (ECG) abnormalities was listed for each subject by treatment.

Subject Disposition: A total of 28 healthy subjects (16 men, 12 women) were enrolled in the study and 25 subjects completed the study. Three subjects were withdrawn from the study prematurely: 2 for adverse events (1 because of pleural infection and 1 because of nausea and vomiting), and 1 for consent withdrawal (reason unknown).

Pharmacokinetic Results:

1. Demographics

The following subjects were withdrawn from the study:

a. Subject 1003, a 28-year old man, withdrew consent (reason unknown) following dose administration on Day 4 of Period 1 (Sequence BA) and was withdrawn from the study. The subject had received 16 mg TAK-375 on Day 4 and 100 mg fluvoxamine BID Days 1 through 4 prior to discontinuation from the study.
b. Subject 1017, a 35-year old woman, was withdrawn from the study on Day 13 of Period 1 (Sequence BA) because of an adverse event (pleural infection). The subject had received 16 mg TAK-375 on Day 4 and 100 mg fluvoxamine BID on Days 1-4 prior to discontinuation from the study.
c. Subject 1022, a 48-year old woman, was withdrawn from the study on Day 1 of Period 1 (Sequence BA) because of 2 adverse events (nausea and vomiting). This subject had received 100 mg fluvoxamine BID for 2 days prior to discontinuation from the study.

Total			Treatment Sequence	
			AB	BA
Gender n (%)	Male	16 (57.1)	8 (57.1)	8 (57.1)
	Female	12 (42.9)	6 (42.9)	6 (42.9)
Race n (%)	Caucasian	16 (57.1)	8 (57.1)	8 (57.1)
	Oriental	1 (3.6)	0 (0)	1 (7.1)
	Black	6 (21.4)	3 (21.4)	3 (21.4)
	Hispanic	1 (3.6)	0 (0)	1 (7.1)
	Native American	1 (3.6)	1 (7.1)	0 (0)
	Other	3 (10.7)	2 (14.3)	1 (7.1)
Age (yrs)	N	28	14	14
	Mean (SD)	34.64 (10.12)	32.71 (9.68)	36.57 (10.53)
	Median	34	34	33.50
	Min-Max	20-54	20-54	21-52
Weight (kg)	N	28	14	14
	Mean (SD)	76.46 (15.33)	80.68 (12.80)	72.24 (16.91)
	Median	79.32	79.55	76.36
	Min-Max	45.91-100.91	51.36-100.91	45.91-94.09
Height (cm)	N	28	14	14
	Mean (SD)	175.80 (10.59)	179.71 (10.47)	171.90 (9.51)
	Median	176.53	179.07	173.99
	Min-Max	157.48-194.31	160.02-194.31	157.48-184.15
BMI (kg/m2)	N	28	14	14
	Mean (SD)	24.59 (3.77)	25.01 (3.62)	24.16 (4.01)
	Median	24.59	25.67	24.01
	Min-Max	17.22-32.49	17.22-31.67	18.51-32.49

2. Based on the results of the analysis of variance (ANOVA) for the pairwise comparisons of the predose fluvoxamine plasma concentrations on Days 2, 3, and 4, steady state was not attained by Day 4 for both the AM and the PM concentrations.

3. Based on the ratio of the LS means for serum unchanged TAK-375, there were statistically significant increases in AUC(0-inf) of approximately 190-fold (P<0.0010), and in Cmax of approximately 70-fold (P<0.0010) when TAK-375 was coadministered with fluvoxamine compared to TAK-375 alone. The increase in AUC(0-inf) with coadministration was also associated with a 99.6% reduction in apparent oral clearance (CL/F of 18.73 L/hr with coadministration of fluvoxamine vs. 4368.26 L/hr when administered alone). Mean Tmax was delayed by about 16 minutes with coadministration of fluvoxamine compared to TAK-375 alone, and the difference was statistically significant (P=0.0037). The ANOVA indicated a statistically significant treatment difference in λz (P<0.0010) and the mean T1/2 values increased by approximately 2-fold (4.12 h compared to 1.34 h) when TAK-375 was coadministered with fluvoxamine.

Summary Statistics and ANOVA Results of Serum TAK-375 Pharmacokinetic Parameters by Treatment :

Parameter (Units)	Trt[a]	N	Mean (SD)	LS Mean	Treatment Comparisons[b] Ratio (B/A) (%)	90% CI for Ratio (%)	P Value
AUC(0-inf) (ng•h/mL)	A	24	7.98 (8.96)	5.076	18987.20	(14078.54 - 25607.33)	<0.0010
	B	24	1021.19 (393.24)	963.722	-	-	-
AUC(0-t) (ng•h/mL)	A	25	7.44 (8.57)	4.647	20955.75	(15264.42 - 28769.10)	<0.0010
	B	25	1015.42 (379.87)	973.888	-	-	-
Cmax (ng/mL)	A	25	6.23 (6.85)	3.860	7211.72	(5262.06 - 9883.75)	<0.0010
	B	25	281.24 (95.19)	278.375	-	-	-
T1/2 (h)	A	24	1.34 (0.69)	-	-	-	<0.0010[c]
	B	24	4.12 (1.15)	-	-	-	-
Tmax (h)	A	25	0.74 (0.31)	0.719	-	-	0.0037
	B	25	1.00 (0.34)	0.989	-	-	-
CL/F (L/h)	A	24	4368.26 (3439.36)	-	-	-	-
	B	24	18.73 (9.22)	-	-	-	-

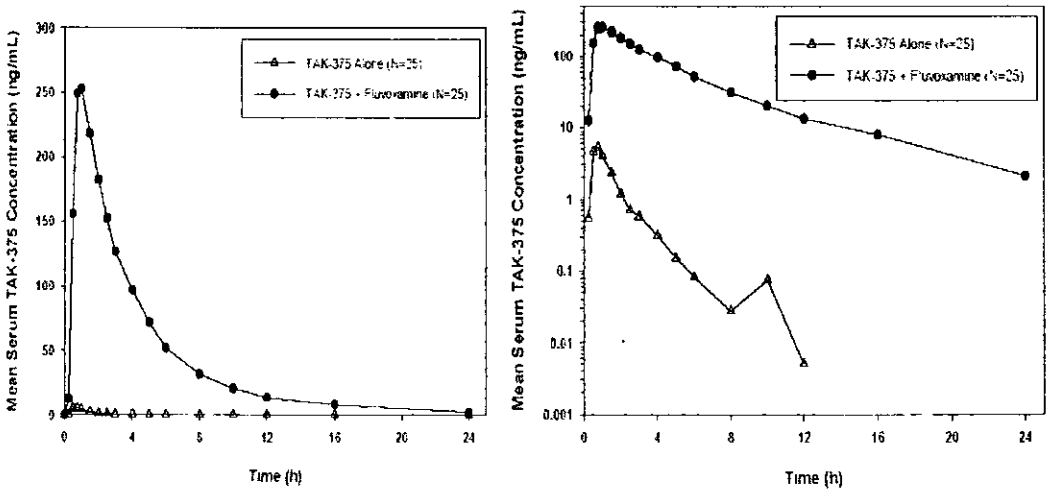
4. Urine Pharmacokinetics of Unchanged TAK-375

a. No ANOVA comparisons were performed to assess treatment differences for the urine pharmacokinetic parameters. Renal elimination of TAK-375 was negligible. Only a small fraction of unchanged TAK-375 (0.000%-0.001% for TAK-375 alone and 0.167%-0.3095% for TAK-375 in combination with fluvoxamine) was recovered in urine within 24 hours.

b. Quantifiable urine concentrations of unchanged TAK-375 were found in 1 of 25 subjects when TAK-375 was taken alone, compared to 25 of 25 subjects when TAK-375 was coadministered with fluvoxamine.

c. Unchanged TAK-375 was excreted within 0 to 4 hours for TAK-375 alone and 0 to 24 hours for TAK-375 in combination with fluvoxamine. The CLr of unchanged TAK-375 was 0.0034 mL/min (range = [ ] mL/min) and 0.2804 mL/min (range = [ ] mL/min) when TAK-375 was taken alone and in combination with fluvoxamine, respectively.

Mean Serum Concentration-Time Profiles for Unchanged TAK-375 by Treatment (Linear and Semi-log Plots)



5. Metabolite M-I

Table 11c Summary Statistics and ANOVA Results of Serum Metabolite M-I Pharmacokinetic Parameters by Treatment

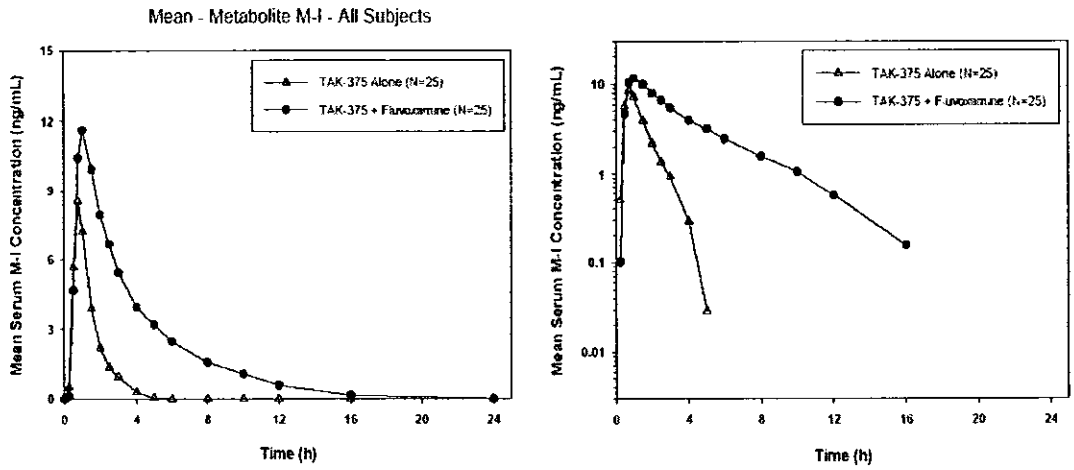
Parameter (Units)	Treatment[a]	N	Mean (SD)	Treatment Comparisons[b] LS Mean	Ratio (B/A) (%)	90% CI for Ratio (%)	P Value
AUC(0-inf) (ng•h/mL)	A	25	11 526 (2.9636)	11.353	397.86	(355.63-445.11)	<0.0010
	B	25	45 807 (12.308)	45.170	-	-	-
AUC(0-t) (ng•h/mL)	A	25	10.733 (2.907)	10.560	386.85	(344.32-434.63)	<0 0010
	B	25	41.613 (11.686)	40.850	-	-	-
Cmax (ng/mL)	A	25	9 512 (2.945)	9.345	128 05	(111.36-147 24)	0.0059
	B	25	12.255 3.976)	11 967	-	-	-
T1/2 (h)	A	25	0.83 (0.26)	-	-	-	<0.0010[c]
	B	25	3.80 (1.49)	-	-	-	-
Tmax (h)	A	25	0 81 (0.22)	0.798	-	-	0 0063
	B	25	1.05 (0.35)	1.038	-	-	-

[a] Treatment A. 16 mg TAK-375 alone (reference)
Treatment B. 16 mg TAK-375 with 100 mg fluvoxamine BID (test)

[b] Based on ANOVA model including fixed effects for sequence, gender, period, treatment, sequence*gender, and random effect subject within sequence*gender

[c] The P-value provided in this table is derived from the statistical analysis of λz.

Source of Data: Table 14.3.2, Table 14.5.2



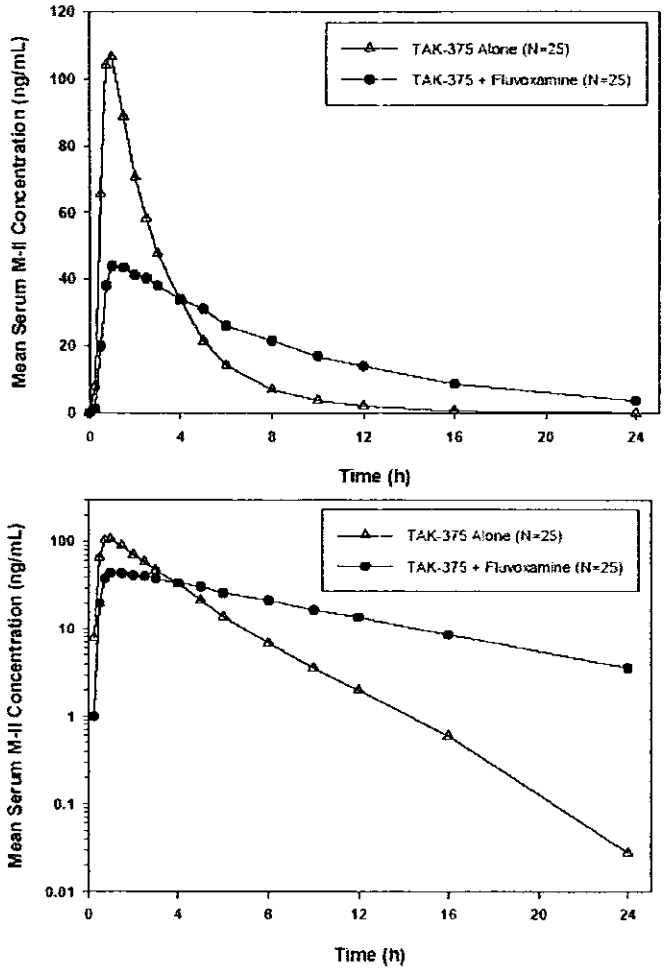
. M-I, AUC(0-inf) increased 298% (P<0.0010), and Cmax increased 28% (P=0.0059) when TAK-375 was coadministered with fluvoxamine compared to TAK-375 alone. Mean Tmax was delayed by about 14 minutes when TAK-375 was coadministered with
fluvoxamine compared to TAK-375 alone, and the difference was statistically significant (P=0.0063).

. Renal elimination of metabolite M-I was negligible. Only a small fraction of metabolite M-I (0.0456%-1.2556%, TAK-375 alone and 0.7920%-4.3997%, TAK-375 in combination with fluvoxamine) was recovered in urine within 24 hours. Quantifiable urine concentrations of metabolite M-I were found in 25 of 25 subjects in both treatments. Metabolite M-I was excreted within 0 to 12 hours for TAK-375 alone and 0 to 24 hours for TAK-375 in combination with fluvoxamine. The mean CLr of metabolite M-I was 219.9519 mL/min (range = [ ] mL/min) and 194.0272 (range [ ] mL/min) when TAK-375 was taken alone and in combination with fluvoxamine, respectively.

6. Metabolite M-II

Based on the ratio of the LS means for serum M-II (the active metabolite of TAK-375), AUC(0-inf) increased 31% (P=0.0017) and Cmax decreased 60% (P<0.0010) when TAK-375 was coadministered with fluvoxamine.

Mean Serum Concentration-Time Profiles for Unchanged M-II by Treatment (Linear and Semi-log Plots)



Summary Statistics and ANOVA Results of Serum Metabolite M-II Pharmacokinetic Parameters by Treatment

Parameter (Units)	Treatment[a]	N	Mean (SD)	Treatment Comparisons[b]			
				LS Mean	Ratio (B/A) (%)	90% CI for Ratio (%)	P Value
AUC(0-inf) (ng•h/mL)	A	25	336.514 (85.320)	333.853	130.63	(114.85-148.58)	0.0017
	B	25	448.683 (147.262)	436.128	-	-	-
AUC(0-t) (ng•h/mL)	A	25	333.147 (84.922)	331.330	121.00	(105.81-138.37)	0.0231
	B	25	411.991 (140.429)	400.901	-	-	-
Cmax (ng/mL)	A	25	117.464 (42.687)	116.046	39.74	(33.57-47.04)	<0.0010
	B	25	48.864 (23.801)	46.119	-	-	-
T1/2 (h)	A	25	2.40 (0.57)	-	-	-	<0.0010[c]
	B	25	6.35 (1.86)	-	-	-	-
Tmax (h)	A	25	0.98 (0.41)	0.906	-	-	0.0013
	B	25	1.77 1.08)	1.713	-		-

. M-II AUC(0-inf) was increased 31% (P=0.0017) and Cmax decreased 60% (P<0.0010) when TAK-375 was coadministered with fluvoxamine. The 90% CIs for the ratios of the LS means for TAK-375 with fluvoxamine relative to TAK-375 alone for AUC(0-inf) and Cmax were (115%-149%) and (34%-47%) respectively. Mean Tmax was delayed by about 47 minutes when TAK-375 was coadministered with fluvoxamine compared to TAK-375 alone, and the difference was statistically significant (P=0.0013). The ANOVA indicated a statistically significant treatment difference for λz (P<0.0010), and mean T1/2 values were approximately 165% greater (6.35 h compared to 2.40 h) when TAK-375 was coadministered with fluvoxamine.

. Renal elimination of metabolite M-II was negligible. Only a small fraction of metabolite M-II (0.0015%-0.2813% [TAK-375] and 0.0000%-0.3092% [TAK-375] in combination with fluvoxamine]) was recovered in urine within 24 hours. Quantifiable urine concentrations of metabolite M-II were found in 25 of 25 subjects when TAK-375 was taken alone compared to 22 of 25 subjects when TAK 375 was coadministered with fluvoxamine. Metabolite M-II was excreted within 0 to 8 hours for TAK-375 alone and 0 to 24 hours for TAK-375 in combination with fluvoxamine. The mean CLr of metabolite M-II was 0.7398 mL/min (range = [ ] mL/min) and 0.5695 mL/min (range = [ ] mL/min) when TAK-375 was taken alone and in combination with fluvoxamine, respectively.

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7. Serum Pharmacokinetics of Metabolite M-III

Mean - Metabolite M-III - All Subjects

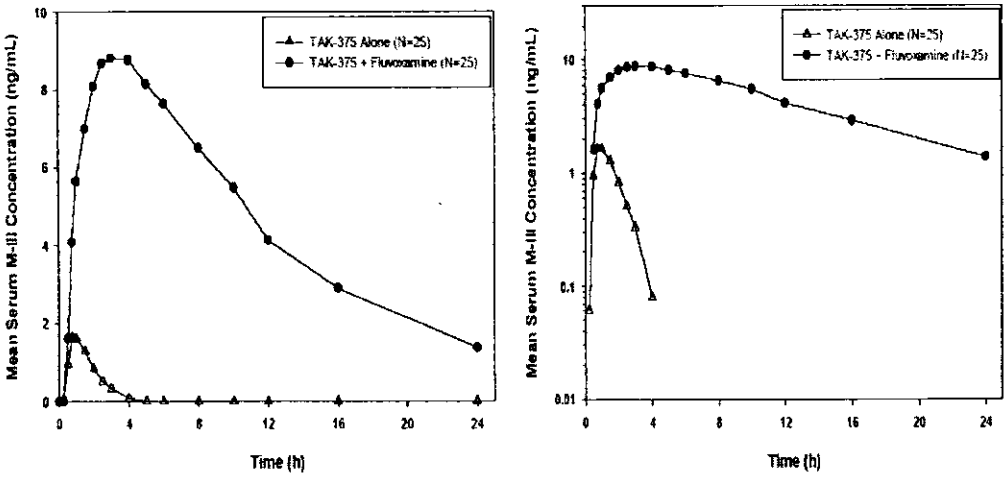


Table 11e **Summary Statistics and ANOVA Results of Serum Metabolite M-III Pharmacokinetic Parameters by Treatment**

Parameter (Units)	Treatment[a]	N	Mean (SD)	Treatment Comparisons[b] LS Mean	Ratio (B:A) (%)	90% CI for Ratio (%)	P Value
AUC(0-inf)	A	9	5 701 (1 808)	5 647	2112 62	(1483 83-3007 88)	<0 0010
(ng•h/mL)	B	9	144 432 (67 739)	119 290	-	-	-
AUC(0-t)	A	21	3 140 (1 927)	2 562	4103 74	(3283 22-5129 31)	<0 0010
(ng•h/mL)	B	21	113 358 (44 368)	105 135	-	-	
Cmax	A	21	2 110 (0 982)	1 890	490 18	(419 39-572 92)	<0 0010
(ng/mL)	B	21	9 771 (3 447)	9 266	-	-	-
T1/2	A	16	1 19 (0 26)	-	-	-	<0 0010[c]
(h)	B	16	7 70 (3 60)	-	-	-	-
Tmax	A	21	0 85 (0 22)	0 845	-	-	<0 0010
(h)	B	21	3 60 (1 22)	3 606	-	-	-

[a] Treatment A: 16 mg TAK-375 alone (reference)
Treatment B: 16 mg TAK-375 with 100 mg fluvoxamine BID (test)

[b] Based on ANOVA model including fixed effects for sequence, gender, period, treatment, sequence*gender, and random effect subject within sequence*gender.

[c] The P-value provided in this table is derived from the statistical analysis of λz.

Source of Data: Table 14 3 2, Table 14 5 4

. M-III AUC(0-inf) was increased 2013% (P<0.0010) and Cmax increased 390% (P<0.0010) when TAK-375 was coadministered with fluvoxamine. The 90% CIs for the ratios of the LS means for TAK-375 with fluvoxamine relative to TAK-375 alone for AUC(0-inf) and Cmax were (1484%-3008%) and (419%-573%) respectively. Mean Tmax was delayed by about 165 minutes when TAK-375 was coadministered with fluvoxamine compared to TAK-375 alone, and the difference was statistically significant (P<0.001). The ANOVA indicated a statistically significant treatment difference for λz (P<0.0010), and mean T1/2 values were approximately 547% greater (7.70 h compared to 1.19 h) when TAK-375 was coadministered with fluvoxamine.

. Renal elimination of metabolite M-III was negligible. Only a small fraction of metabolite M-III (0.0000%-0.0165% for TAK-375 alone and 0.0446%-0.5007% for TAK-375 incombination with fluvoxamine) was recovered in urine within 24 hours. Quantifiable urine concentrations of metabolite M-III were found in 2 of 25 subjects when TAK-375 was taken alone, compared to 25 of 25 subjects when TAK-375 was taken in combination with fluvoxamine. Metabolite M-III was excreted within 0 to 4 hours for TAK-375 alone and 0 to 24 hours for TAK-375 in combination with fluvoxamine. The mean CLr of

metabolite M-III was 0.5215 mL/min (range = [ ] mL/min) and 4.5083 mL/min (range = [ ] mL/min) when TAK-375 was taken alone and in combination with fluvoxamine, respectively.

8. Pharmacokinetic Analyses of Metabolite M-IV

Mean - Metabolite M-IV - All Subjects

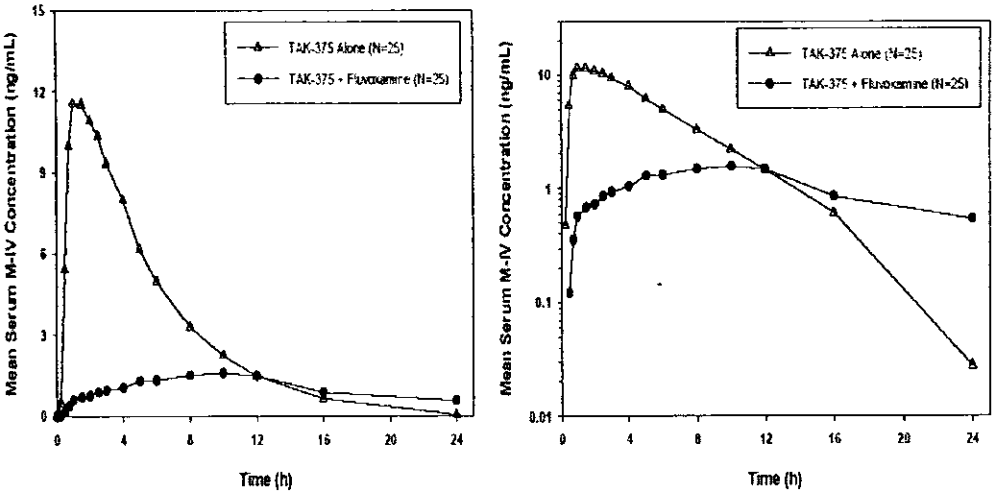


Table 11f **Summary Statistics and ANOVA Results of Serum Metabolite M-IV Pharmacokinetic Parameters by Treatment**

Parameter (Units)	Treatment[a]	N	Mean (SD)	Treatment Comparisons[b] LS Mean	Ratio (B/A) (%)	90% CI for Ratio (%)	P Value
AUC(0-inf)	A	2	74.797 (12.195)	-	-	-	-
(ng•h/mL)	B	2	60.391 (13.189)	-	-	-	-
AUC(0-t)	A	23	71.399 (27.575)	69.428	31.34	(24.74-39.70)	<0.0010
(ng•h/mL)	B	23	26.598 (15.649)	21.759	-	-	-
Cmax	A	23	12.775 (4.622)	12.487	13.26	(10.89-16.15)	<0.0010
(ng/mL)	B	23	1.855 (0.967)	1.656	-	-	-
T1/2	A	4	3.72 (0.11)	-	-	-	-
(h)	B	4	14.17 (12.15)	-	-	-	-
Tmax	A	23	1.26 (0.53)	1.250	-	-	<0.0010
(h)	B	23	9.32 (2.57)	9.325	-	-	-

[a] Treatment A: 16 mg TAK-375 alone (reference)
Treatment B: 16 mg TAK-375 with 100 mg fluvoxamine BID (test)

[b] Based on ANOVA model including fixed effects for sequence, gender, period, treatment, sequence*gender, and random effect subject within sequence*gender.

Source of Data: Table 14.3.2, Table 14.5.5

. M-IV AUC(0-t) was decreased 69% (P<0.001) and Cmax was decreased by about 87% (P<0.001) when TAK-375 was coadministered with fluvoxamine. The 90% CIs for the ratios of the LS means for TAK-375 with fluvoxamine relative to TAK-375 alone for AUC(0-t) and Cmax were (25%-40%) and (11%-16%), respectively. Mean Tmax was delayed by about 520 minutes when TAK-375 was coadministered with fluvoxamine compared to TAK-375 alone, and the difference was statistically significant (P<0.001). Mean T1/2 values were 281% greater (14.17 h compared to 3.72 h) when TAK-375 was coadministered with fluvoxamine.

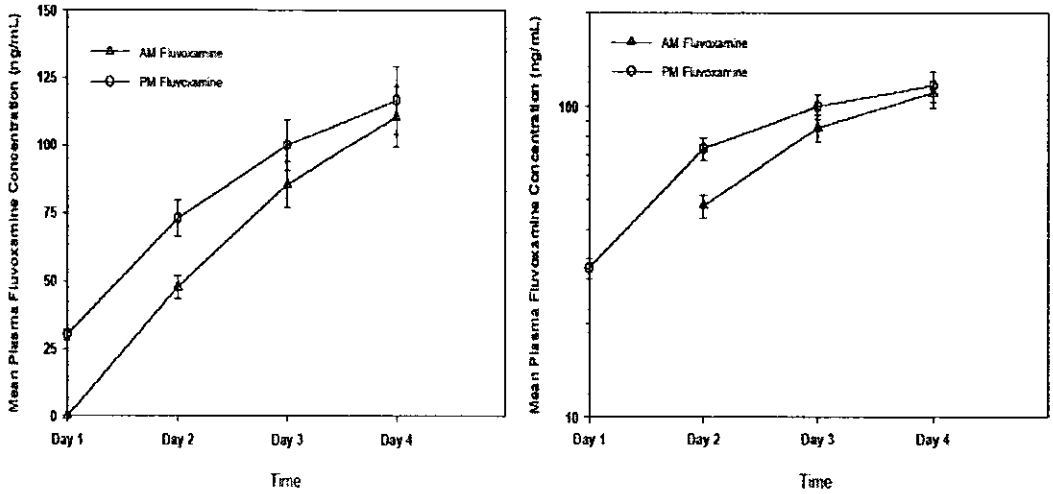
. Renal elimination of metabolite M-IV was negligible. Only a small fraction of metabolite M-IV (1.0836%-6.1198%, TAK-375 alone and 0.3320%-2.6725%, TAK-375 in combination with fluvoxamine) was recovered in urine within 24 hours. Quantifiable urine concentrations of metabolite M-IV were found in 25 of 25 subjects in both treatments. Metabolite M-IV was excreted within 0 to 24 hours in both

treatments. The mean CLr of metabolite M-IV was 144.4496 mL/min (range = [ ] mL/min) and 176.9040 mL/min (range = [ ] mL/min) when TAK-375 was taken alone and in combination with fluvoxamine, respectively.

9. Statistical Models for Fluvoxamine Steady-State Determination

Mean (+/-SE) -Fluvoxamine - All Subjects

Mean Predose Plasma Concentrations of Fluvoxamine Over Time by Treatment for All Subjects (Linear and Semi-log Plots)



Steady-State Analysis of Predose Fluvoxamine Plasma Concentrations

		LS Mean
Guidetime	Day	(ng/mL)a
AM	2	43.970
	3	76.302
	4	98.476
PM	2	67.048
	3	89.519
	4	101.150

aP-values <0.001 for all pairwise comparisons: Day 2 versus Day 3; Day 2 versus Day 4; and Day 3 versus Day 4.
Source of Data: Table 14.6.2

Based on the results of the ANOVA for the pairwise comparisons of the predose fluvoxamine plasma concentrations on Days 2, 3, and 4, steady state was not attained by Day 4 for both the AM and the PM concentrations.

10. Pharmacokinetic Discussion and Conclusion

Data for M-I, M-III, and M-IV are summarized in the table below. Though renal clearance reflected a relevant contribution only to M-I and M-IV elimination, the overall urinary excretion of TAK-375 and metabolites was negligible. Approximately 4.3% and 4.4% of the total dose was excreted into urine as total drug product (TAK-375 + M-I + M-II + M-III + M-IV) when TAK-375 was administered alone and when coadministered with fluvoxamine, respectively.

Overall PK parameters:

Analyte	Parameter (Units)	LS Means		Ratio B/A (%)	90% CI for Ratio (%)	P value
		A_a	B_a			
TAK-375	AUC(0-inf) (ng•h/mL)	5.076	963.722	18987.2	(14078.54 -25607.33)	<0.0010
	Cmax (ng/mL)	3.86	278.375	7211.72	(5262.06 - 9883.75)	<0.0010
	Tmax (h) T1/2 (h)c	0.719 1.15	0.989 3.94			0.0037<0.0010b
M-I	AUC(0-inf) (ng•h/mL)	11.353	45.17	397.86	(355.63 -445.11)	<0.0010
	Cmax (ng/mL)	9.345	11.967	128.05	(111.36 -147.24)	0.0059
	Tmax (h) T1/2 (h)c	0.798 0.85	1.038 3.18			0.0063<0.0010b
M-II	AUC(0-inf) (ng•h/mL)	333.853	436.128	130.63	(114.85 -148.58)	0.0017
	Cmax (ng/mL)	116.046	46.119	39.74	(33.57 -47.04)	<0.0010
	Tmax (h) T1/2 (h)c	0.906 2.28	1.713 5.87			0.0013<0.0010b
M-III	AUC(0-inf) (ng•h/mL)	5.647	119.29	2112.62	(1483.83 - 3007.88)	<0.0010
	Cmax (ng/mL)	1.89	9.266	490.18	(419.39 -572.92)	<0.0010
	Tmax (h) T1/2 (h)c	0.845 1.13	3.606 5.21			<0.0010 <0.0010b
M-IV	AUC(0-inf) (ng•h/mL)	ND	-	-	-	-
	AUC(0-t) (ng•h/mL)	69.428	21.759	31.34	(24.74 -39.70)	<0.0010
	Cmax (ng/mL)	12.487	1.656	13.26	(10.89 -16.15)	<0.0010
	Tmax (h)	1.25	9.325			<0.0010
	T1/2 (h)c	ND	-	-	-	-

Note. LS means ratios and 90% confidence intervals on ratios are calculated by exponentiating the values of the log transformed AUCs and Cmax. For Metabolite M-IV AUC(0-t) was used instead of AUC(0-inf) due to insufficient data.
ND: Not determined due to insufficient data
a Treatment A: 16 mg TAK-375 alone (reference) Treatment B: 16 mg TAK-375 with 100 mg fluvoxamine BID (test)
b The P value provided in this table is derived from the statistical analysis of λ_z.
c Computed using the equation $T1/2 = \ln(2)/\lambda_z$.

11. Safety Results:

The Applicant reported the following safety assessment. The incidence of adverse events (AEs) was greater during coadministration of TAK-375 and fluvoxamine than during administration of TAK-375 alone. The number of subjects with adverse events possibly or probably related to study medication was greater when TAK-375 was administered alone than when TAK-375 was co-administered with fluvoxamine (19 of 25 subjects versus 17 of 28 subjects, respectively) .

The most common adverse events reported were fatigue for subjects in Treatment A and nausea for subjects in Treatment B. There were no serious adverse events. No adverse events were considered severe, and no withdrawals from the study were considered to be related to study medication. Two subjects were withdrawn from the study due to adverse events (1 because of pleural infection and 1 because of nausea and vomiting) unrelated to study medication.

	Number (%) Subjects	
	16 mg TAK-375 alone (N=25)	16 mg TAK-375 with fluvoxamine (N=28)
With any AE	20 (80.0)	27 (96.4)
With any drug-related AE	19 (76.0)	17 (60.7)
Discontinued due to AE	0 (0.0)	2 (7.1)
With any serious AE (SAE)	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)

Changes in mean laboratory parameters (hematology, serum chemistry and urinalysis) were generally minimal throughout the study, and mean laboratory values were similar to those observed at Baseline. Two subjects had laboratory values (both abnormal liver function tests) that were considered clinically significant by the Investigator and were reported as adverse events. One of these instances was considered to be possibly related to study medication. No clinically significant vital sign values or changes in vital signs parameters were reported during the study, and no clinically significant ECG findings or changes in ECG parameters were reported.

Brief Summary of Adverse Events

All subjects (28/28) experienced 164 separate occurrences of adverse events (146 unique events) during the study. Two other events occurred in the study, prior to the first dose of study medication. Of the 28 subjects who experienced adverse events, 25 subjects experienced 57 adverse events that were considered possibly or probably related to study medication during 1 or more treatment periods. No adverse events were considered by the Investigator to be definitely related to study medication.

The incidence of adverse events was slightly greater during coadministration of TAK-375 and fluvoxamine (Treatment B) than during administration of TAK-375 alone (Treatment A); Of these, 19 subjects experienced adverse events that were considered possibly or probably related to study medication. During Treatment B, 27 of 28 subjects (96.4%) experienced at least 1 adverse event. Of these, 17 subjects experienced adverse events that were considered possibly or probably related to study medication.

The number of subjects reporting adverse events during Treatment A was highest in the general disorders and administration site conditions class (15 of 25 subjects [60.0%]). The number of subjects reporting adverse events during Treatment B was highest in the nervous system organ class (21 of 28 subjects [75.0%]). The most common adverse event reported was fatigue for subjects in Treatment A (13 of 25 subjects [52.0%]) and nausea for subjects in Treatment B (16 of 28 subjects [57.1%]); fatigue can be considered an expected pharmacological effect of TAK-375. All adverse events were either mild or moderate in severity. Two subjects were withdrawn from the study because of 3 adverse events, but none of these adverse events were considered to be related to study medication. There were no serious adverse events during the study, and no deaths occurred during the study.

Table 12a Adverse Events by Preferred Term by Treatment

System Organ Class Preferred Term	TAK-375 (16 mg) Alone Overall N=25 (%)	TAK-375 (16 mg) plus fluvoxamine Overall N=28 (%)
Overall	**20 (80.0)**	**27 (96.4)**
Eye Disorders	**1 (4.0)**	**1 (3.6)**
Dry eye NOS	---	1 (3.6)
Vision blurred	1 (4.0)	---
Gastrointestinal Disorders	**3 (12.0)**	**16 (57.1)**
Constipation	---	2 (7.1)
Diarrhoea NOS	1 (4.0)	2 (7.1)
Dry mouth	---	4 (14.3)
Dyspepsia	---	2 (7.1)
Dysphagia	---	2 (7.1)
Flatulence	---	1 (3.6)
Hiccups	---	1 (3.6)
Loose stools	---	3 (10.7)
Nausea	2 (8.0)	16 (57.1)
Vomiting NOS	---	5 (17.9)
General Disorders and Administration Site Conditions	**15 (60.0)**	**14 (50.0)**
Fatigue	13 (52.0)	14 (50.0)
Lethargy	1 (4.0)	---
Weakness	1 (4.0)	---
Infections and Infestations	**3 (12.0)**	**4 (14.3)**
Herpes simplex	---	1 (3.6)
Pleural infection NOS	---	1 (3.6)
Sinusitis NOS	1 (4.0)	---
Upper respiratory tract infection NOS	2 (8.0)	2 (7.1)
Injury, Poisoning and Procedural Complications	**0 (0.0)**	**2 (7.1)**
Therapeutic agent toxicity	---	2 (7.1)
Investigations	---	**1 (3.6)**
Liver function tests NOS abnormal	---	1 (3.6)
Nervous System Disorders	**10 (40.0)**	**21 (75.0)**
Aura NOS	---	2 (7.1)
Disturbance in attention	3 (12.0)	3 (10.7)
Dizziness	2 (8.0)	5 (17.9)
Dystonia	---	2 (7.1)
Headache NOS	3 (12.0)	8 (28.6)
Paraesthesia	---	2 (7.1)
Somnolence	5 (20.0)	6 (21.4)
Tremor	---	1 (3.6)
Tunnel vision	---	2 (7.1)
Psychiatric Disorders	**4 (16.0)**	**6 (21.4)**
Abnormal dreams	1 (4.0)	1 (3.6)
Dysphoria	1 (4.0)	4 (14.3)
Insomnia	1 (4.0)	1 (3.6)
Irritability	1 (4.0)	1 (3.6)
Reproductive System and Breast Disorders	**1 (4.0)**	---
Menstruation irregular	1 (4.0)	---

Table 12a **Adverse Events by Preferred Term by Treatment (continued)**

System Organ Class Preferred Term	TAK-375 (16 mg) Alone Overall N=25 (%)	TAK-375 (16 mg) plus fluvoxamine Overall N=28 (%)
Respiratory, Thoracic, and Mediastinal Disorders	---	**3 (10.7)**
Cough	---	1 (3.6)
Epistaxis	---	1 (3.6)
Postnasal drip	---	1 (3.6)
Skin and Subcutaneous Tissue Disorders	---	**5 (17.9)**
Acne aggravated	---	2 (7.1)
Hyperkeratosis palmaris and plantaris	---	1 (3.6)
Photosensitivity reaction NOS	---	2 (7.1)
Rash pruritic	---	1 (3.6)
Surgical and Medical Procedures	---	**1 (3.6)**
Conjunctival injection	---	1 (3.6)
Vascular Disorders	**1 (4.0)**	**1 (3.6)**
Haematoma NOS	---	1 (3.6)
Hot flushes NOS	1 (4.0)	0 (0.0)

Analysis of Adverse Events

Of the 28 subjects who experienced adverse events, 25 subjects experienced 57 adverse events during the study that were considered possibly or probably related to study medication. The most common adverse event reported that was considered possibly related to study medication was fatigue (13 of 25 subjects [52.0%] in Treatment A and 10 of 28 subjects [35.7%] in Treatment B, respectively), which is an expected pharmacological effect of TAK-375.

Adverse event severity

Overall, the majority of subjects experienced adverse events that were mild in severity. The incidence of mild adverse events was greater in Treatment B (19 of 25 subjects [76.0%] in Treatment A and 26 of 28 subjects [92.9%] in Treatment B). The incidence of adverse events that were moderate in severity was nearly the same between the 2 treatment groups (1 of 25 subjects [4.0%] during Treatment A and 1 of 28 subjects [3.6%] during Treatment B). No adverse events were classified as severe.

Clinical Laboratory Evaluation

Evaluation of Each Laboratory Parameter

A total of 13 subjects had abnormal hematology results, 22 had abnormal serum chemistry results, and 8 had abnormal urinalysis laboratory results at Screening. None of these abnormalities were considered by the Investigator to be clinically significant, and none precluded entry into the study. Likewise, a total of 12 subjects had abnormal hematology results, 24 had abnormal serum chemistry results, and 9 had abnormal urinalysis laboratory results at Day -1 Period 1 of the study prior to administration of study medication. These abnormal results consisted predominantly of small deviations from the normal range. None of the abnormalities at Screening or Day -1 of Period 1 were considered to be clinically significant or resulted in an adverse event. For most clinical laboratory parameters, Baseline was defined as the last observation taken prior to the first dose of study medication in each treatment period. For triglycerides, total insulin, cholesterol, and serum glucose, the Screening value was used as Baseline, since nonfasting and fasting laboratory values were not comparable. The study exit values corresponded to the fifth day in each treatment period (Day 5 in Period 1 and Day 23 in Period 2).

Hematology

Changes in mean hematology parameters were minimal throughout the study, and mean hematology results on Day 5 and Day 23 were generally similar to those observed at baseline for both Treatments A and B. The only notable changes in mean hematology parameters occurred during Treatment A and included decreases in WBC count and absolute neutrophils; mean values decreased by approximately 26% and 30%, respectively. These changes were not clinically significant, however, and mean values remained within normal ranges. Generally, the number of subjects experiencing changes from normal to either high or low

hematology clinical laboratory values was small. The hematology parameters in which 2 or more subjects experienced decreases from Baseline to Exit were WBC count and absolute neutrophils in Treatment A and WBC count, RBC count, and hematocrit in Treatment B. The only hematology parameter in which 2 or more subjects experienced increases from Baseline to Exit was monocytes in Treatment B. No hematology values were reported as adverse events.

Serum Chemistry
Changes in mean serum chemistry values were generally minimal throughout the study, and mean serum chemistry results on Day 5 and Day 23 were generally similar to those observed at Baseline for both Treatments A and B. Notable trends occurred in total bilirubin, which increased by 98% and 62% in Treatments A and B, respectively and total insulin, which decreased by 59 % and 76% in Treatments A and B, respectively. These changes were not clinically significant, however, and mean values remained within normal ranges. Generally, the number of subjects experiencing changes from normal to either high or low serum chemistry clinical laboratory values was small.

Urinalysis
Overall, urinalysis results did not change throughout the study, with those results on Day 5 and Day 23 being similar to those observed at Baseline. The only urinalysis parameter in which 2 or more subjects experienced a shift from a normal Baseline value to an abnormal postdose value was ketones; 3 subjects in Treatment B experienced a normal to high shift. There were no clinically significant urinalysis results in any of the subjects.

Vital Signs
There were no clinically noteworthy changes in any of the vital sign parameters. No subject experienced a vital sign change that was reported as an adverse event or that caused the subject to withdraw prematurely from the study.

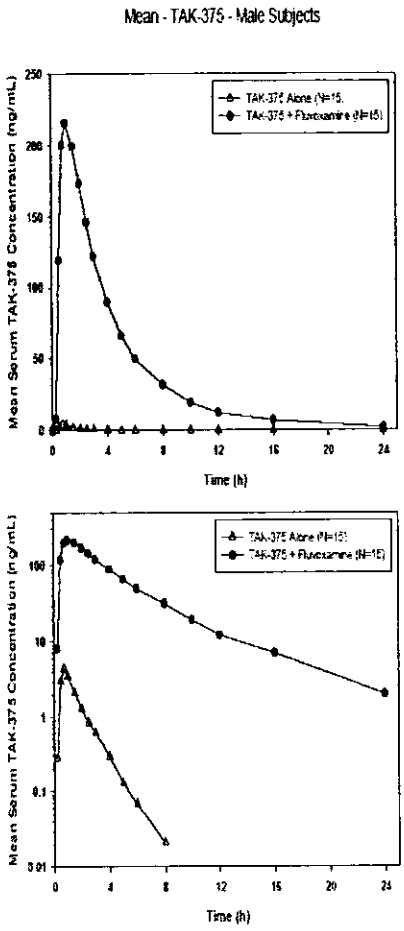
Vital Sign Changes Over Time
There were no clinically noteworthy changes observed in any of the vital sign parameters. Mean pulse rate tended to decrease slightly for both treatment groups, more so during Treatment B. These decreases were not considered clinically relevant.

Electrocardiograms
A total of 18 subjects had abnormal ECG tracings at Baseline and/or while receiving study medication. These abnormalities included S1, S2, and S3 pattern; sinus arrhythmia; left atrial enlargement; high QRS voltage, short QT, left ventricular hypertrophy; early transition; incomplete right bundle branch block; sinus tachycardia; sinus bradycardia; borderline first degree atrioventricular (AV) block; t- and st-wave abnormalities; RSR; atrial premature complex; and occasional premature atrial contraction (PAC). None of these abnormalities were considered to be clinically significant by the Investigator, and no adverse events were recorded for ECG abnormalities.

Appendix

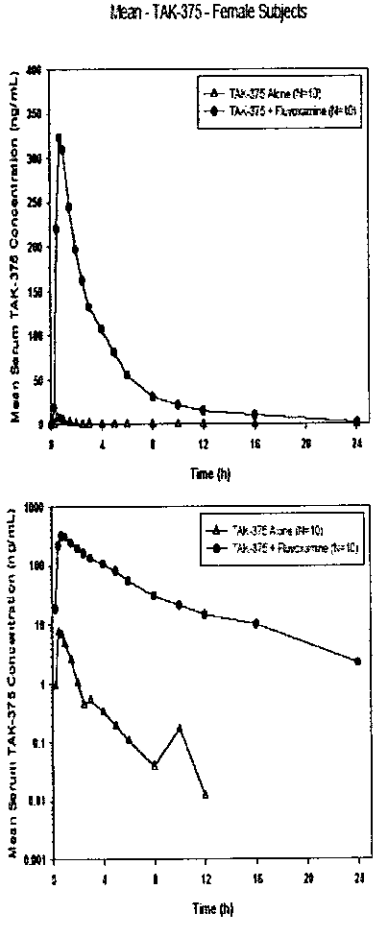
Figures:

Figure 14.1.1.2 Mean Serum Concentrations of TAK-375 Over Time by Treatment in Male Subjects



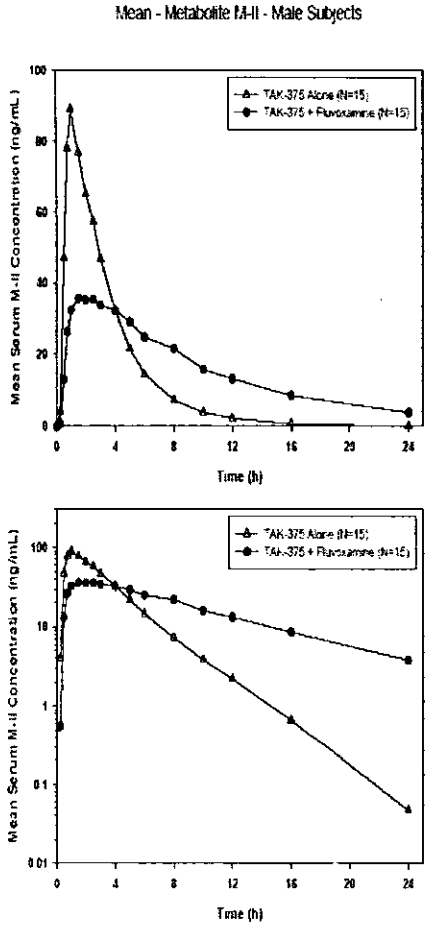
The following time points at 1.5 hr for subjects 1001 and 1003 period 1 and 2.5 hr for subjects 1021 and 1021 period 2 were excluded as outliers from the mean plots due to possible sample switches.

Figure 14.1.1.3 Mean Serum Concentrations of TAK-375 Over Time by Treatment in Female Subjects



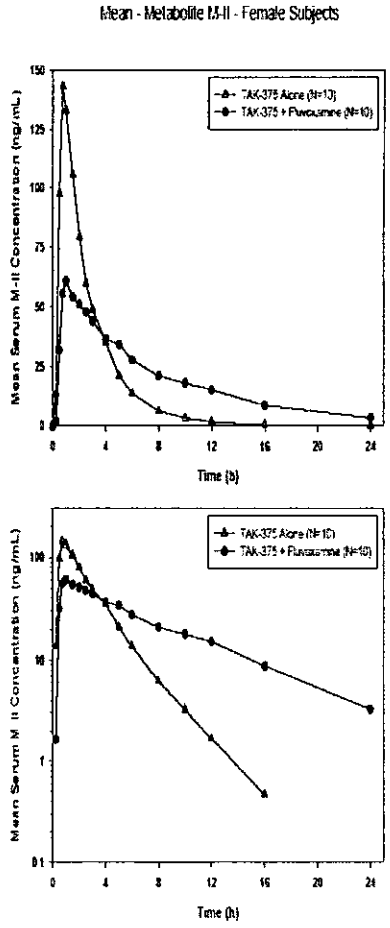
The following time points at 1.5 hr for subjects 1001 and 1005 period 1 and 2.5 hr for subjects 1021 and 1021 period 2 were excluded as outliers from the mean plots due to possible sample switches.

Figure 14.1.3.2 Mean Serum Concentrations of Metabolite M-II of TAK-375 Over Time by Treatment in Male Subjects



The following time points at 1.5 hr for subjects 1001 and 1003 period 1 and 2.5 hr for subjects 1021 and 1021 period 2 were excluded as outliers from the mean plots due to possible sample switches.

Figure 14.1.3.3 Mean Serum Concentrations of Metabolite M-II of TAK-375 Over Time by Treatment in Female Subjects



The following time points at 1.5 hr for subjects 1001 and 1003 period 1 and 2.5 hr for subjects 1001 and 1021 period 2 were excluded as outliers from the mean plots due to possible sample switches

Figure 14.2.1 Mean and Individual Serum Cmax, AUC(0-t) and AUC(0-inf) of TAK-375 by Treatment

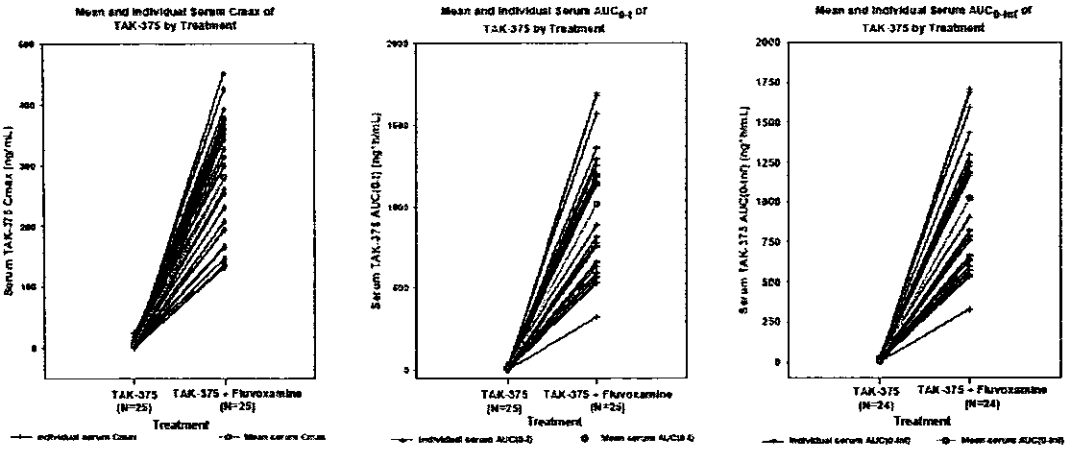


Figure 14.2.3 Mean and Individual Serum Cmax, AUC(0-t) and AUC(0-inf) of Metabolite M-II of TAK-375 by Treatment

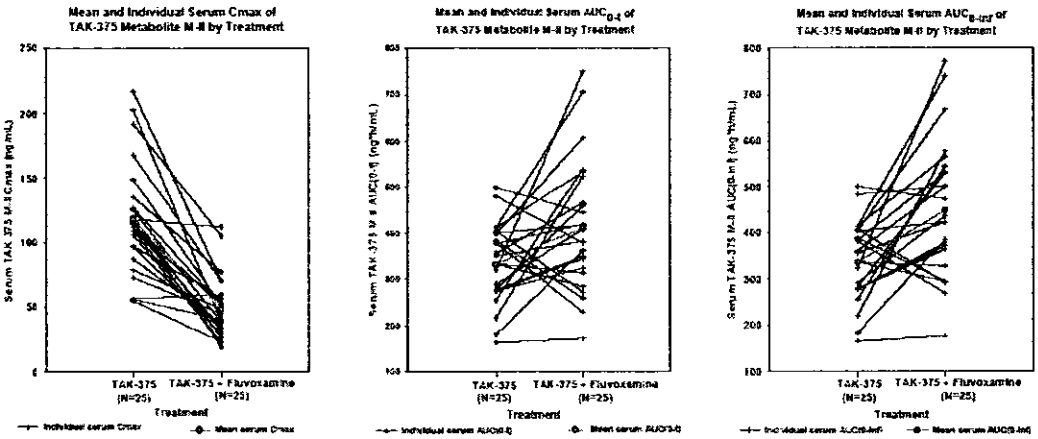
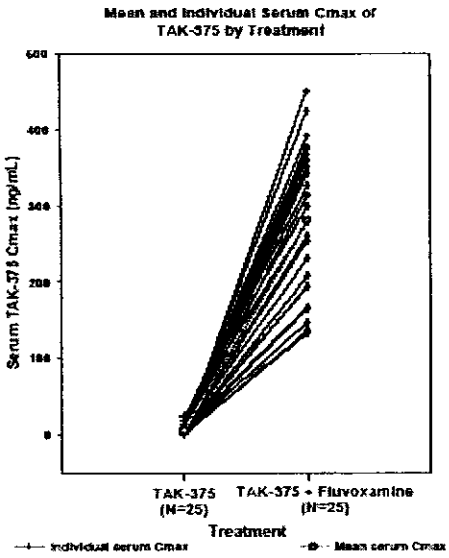
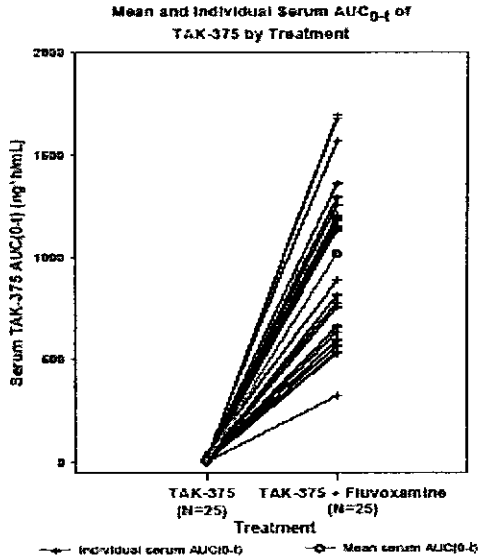


Figure 14.2.1 Mean and Individual Serum Cmax, AUC(0-t) and AUC(0-inf) of TAK-375 by Treatment





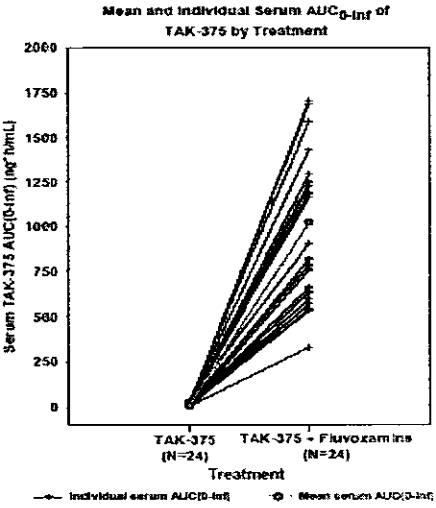
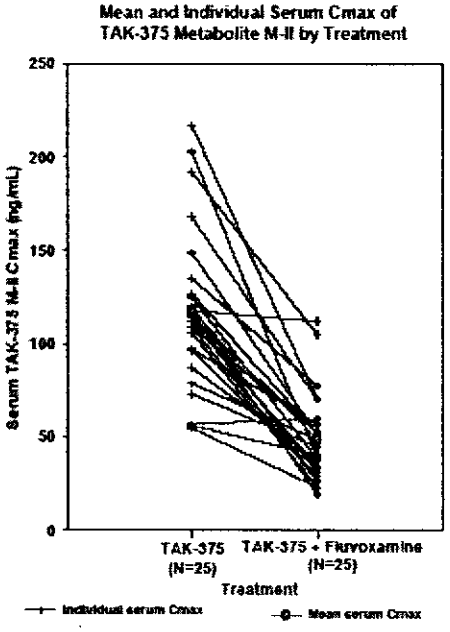
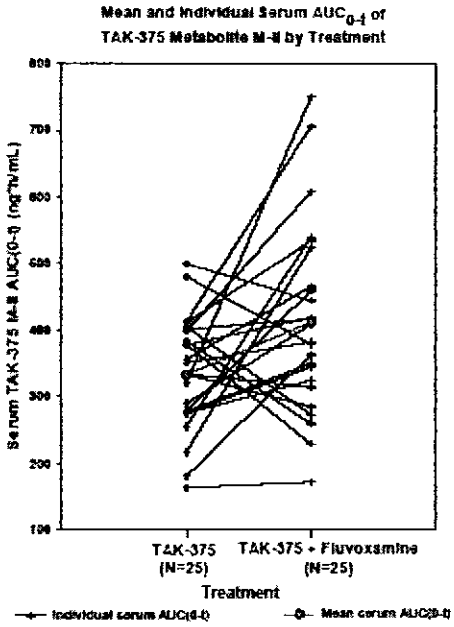
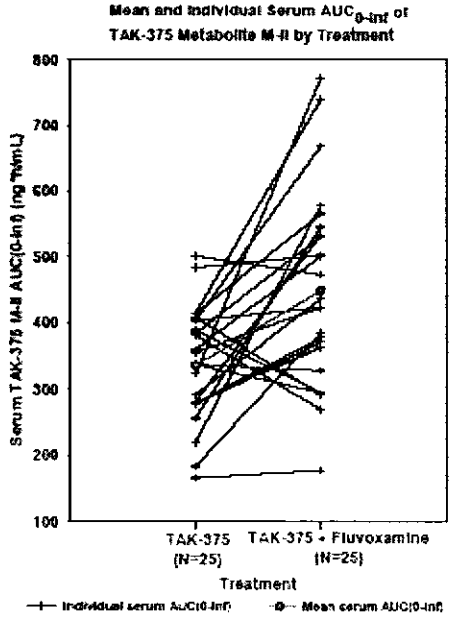


Figure 14.2.3 Mean and Individual Serum Cmax, AUC(0-t) and AUC(0-inf) of Metabolite M-II of TAK-375 by Treatment







4.3.2 Hepatic Study

CLINICAL PROTOCOL FOR A TAK-375 SINGLE AND MULTIPLE DOSE PHARMACOKINETIC EVALUATION IN SUBJECTS WITH AND WITHOUT HEPATIC IMPAIRMENT (01-02-TL-375-029)

OBJECTIVES

Primary:

The primary objective of this study was to evaluate the pharmacokinetic profile of single and multiple oral doses of ramelteon in subjects with varying degrees of hepatic impairment.

Secondary:

The secondary objective of this study was to evaluate the safety and tolerability of single and multiple oral doses of ramelteon in subjects with varying degrees of hepatic impairment.

METHODOLOGY

This was an open-label, single and multiple dose, pharmacokinetic study with a single treatment sequence. A schematic of the study design follows:

		Treatment Period				
Screening	Baseline	Single Dose of Ramelteon 16 mg	Washout	Multiple Dose of Ramelteon 16 mg	Pharmacokinetic Sampling	Posttreatment or Early Termination
Days -28 to -2	Day -1	Day 1	Days 2 to 3	Days 4 to 8	Day 9	Day 10

Schematic of Study Design

		Treatment Period				
Screening	Baseline	Single Dose of Ramelteon 16 mg	Washout	Multiple Dose of Ramelteon 16 mg	Pharmacokinetic Sampling	Posttreatment or Early Termination
Days -28 to -2	Day -1	Day 1	Days 2 to 3	Days 4 to 8	Day 9	Day 10

Schedule of Assessments

			Treatment Period								Posttreatment or Early Termination
Procedure or Observation	Screening	Baseline	Single Dose	Washout			Multiple Dose				
Day	-28 to -2	-1	1	2	3	4	5-6	7	8	9	10
Informed consent	X										
Medical history/ demographics	X										
Baseline conditions/ symptoms		X									
Physical examination (including weight and vital signs)	X	X									X
Height/ BMI	X	X									
12-lead ECG	X										X
Clinical laboratory tests	X	X									X
Hepatitis panel	X										
HIV	X										
Urine drug screen and serum alcohol screen	X	X									
Serum pregnancy test (if female of childbearing potential)	X	X									
Overnight fast		X			X	X	X	X			
Ramelteon dosing			X			X	X	X	X		
In-house Vital signs			X	X					X	X	
Pharmacokinetic blood samples			X	X	X		X	X	X	X	X
Pharmacokinetic urine samples		X	X	X	X			X	X	X	
Creatinine clearance										X	X
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Subject confinement		X	X	X	X	X	X	X	X	X	

BMI indicates body mass index; HIV, human immunodeficiency virus.

Single Dosing (Day 1)

Study drug administration.

Vital signs at 0 (predose), and 1 and 4 hours postdose.

Collection of pharmacokinetic blood samples at 0 (predose), 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, and 12 hours postdose.

Collection of urine for pharmacokinetic measurement from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose.

Washout (Day 2)

Vital signs at 24 hours postdose.

Collection of pharmacokinetic blood samples at 24 hours postdose.

Collection of urine for pharmacokinetic measurement: finished 12 to 24 hours collection and started 24 to 48 hours postdose collection.

Washout (Day 3)

Collection of pharmacokinetic blood samples at 48 hours postdose.

Collection of urine for pharmacokinetic measurement: finished 24 to 48 hour postdose collection.

Overnight fast of at least 8 hours.

Multiple Dosing (Day 4 through Day 8)

Day 4

Study drug administration.

Overnight fast of at least 8 hours.

Day 5 to Day 6

Study drug administration.

Collection of pharmacokinetic samples for measurement of predose concentrations.

Overnight fast of at least 8 hours.

Day 7

Study drug administration.

Collection of pharmacokinetic blood samples for measurement of predose concentrations.

-10 to 0 hour urine collection started for pharmacokinetic analysis.

Overnight fast of at least 8 hours.

Day 8

Study drug administration.

Vital signs at 0 (predose) and 1 and 4 hours postdose.

Collection of pharmacokinetic blood samples at 0 (predose), 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, and 12 hours postdose.

Collection of urine for pharmacokinetic measurement from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose.

Day 9

Vital signs at 24 hours postdose.

Collection of pharmacokinetic blood samples at 24 hours postdose.

Collection of urine: finished 12 to 24 hour collection for pharmacokinetic measurement and started 24 to 48 hour postdose collection for creatinine clearance.

Pharmacokinetic Sampling

Blood samples (7 mL) for measurement of serum ramelteon and its metabolites were collected on Day 1 and Day 8 at 15 minutes predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours postdose.

Serum trough samples were collected on Day 5 through Day 7 at 15 minutes predose. Urine samples, for the analysis of ramelteon and its metabolites, were collected at -10 to 0 hour predose, and 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hours postdose relative to dosing on Day 1, and at –10 to 0 hours predose, and 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose relative to dosing on Day 8.

Discussion of Study Design
The study was designed to compare the pharmacokinetics of ramelteon in subjects with impaired liver function to healthy matched subjects with normal hepatic function. The healthy control subjects were matched to the hepatic-impaired subjects by selected demographic and baseline characteristics to minimize physiological factors known to alter the pharmacokinetics of a drug. In order to have a sample of subjects with a reasonable spectrum of mild to moderate hepatic impairment, subjects with liver cirrhosis were recruited and stratified according to the Child-Pugh classification system, namely scores of 5 to 6 or 7 to 9 corresponded to mild or moderate dysfunction, respectively. Subjects with severe hepatic impairment were not studied. Additionally, the mean serum T1/2s of ramelteon and its metabolites (1 to 2 hours, and 1 to 5 hours, respectively, in healthy subjects) were used to determine the length of the washout between the single and multiple dose administrations of ramelteon.

Diagnosis and Main Criteria for Inclusion:
To qualify for study participation, subjects must have had/been: men or nonpregnant, nonlactating women; 18 to 79 years of age, inclusive; at least 50 kg (110 pounds) with a body mass index (BMI) less than or equal to 40 kg/m2; able to comprehend and willing to sign an informed consent form; negative urine test results for selected substances of abuse at Screening and at Check-in on Study Day -1; a negative human immunodeficiency virus (HIV) antibody test result at Screening; and in good health as determined by the investigator (healthy matched subjects only). Additionally, healthy matched subjects must have had a negative hepatitis panel test results at Screening (or proof of hepatitis B vaccination if positive for hepatitis B surface antibody), and subjects with hepatic impairment must have had a clinical diagnosis of cirrhosis and been classified as having mild or moderate hepatic impairment as defined by the Child-Pugh classification system. Healthy subjects were matched with hepatically impaired subjects on the basis of race, gender, age (±10 years), weight (±30%), and smoking status.

Study Drug, Dose, Mode of Administration, and Lot Number:
Lot Number
Ramelteon 16 mg tablet, oral Z515A021

Duration of Treatment:
The study duration was 10 days: a single dose of ramelteon 16 mg on Day 1, followed by a 2-day washout period on Day 2 through Day 3, a once daily dose of ramelteon 16 mg on Day 4 through Day 8, pharmacokinetic sampling on Day 9, and a posttreatment day on Day 10. Subjects received a single 16 mg ramelteon dose under fasting conditions on the morning of Day 1 followed by a 2-day washout on Day 2 and Day 3. On the mornings of Day 4 through Day 8, 16 mg of ramelteon was administered daily under fasting conditions.

Treatments Administered
Each subject received ramelteon 16 mg following at least an 8-hour fast on Day 1 and Day 4 through Day 8. Each dose of study drug was administered with approximately 240 mL of room temperature water.

Selection of Doses Used in the Study
A 16 mg dose of ramelteon was selected because it is projected to be the most widely used therapeutic dose.

Drug Concentration Measurements
The concentrations of ramelteon and its metabolites (M-I, M-II, M-III, and M-IV) in human serum were measured by [redacted] with a validated concentration range in serum of [redacted] ng/mL for ramelteon and [redacted] ng/mL for its metabolites.

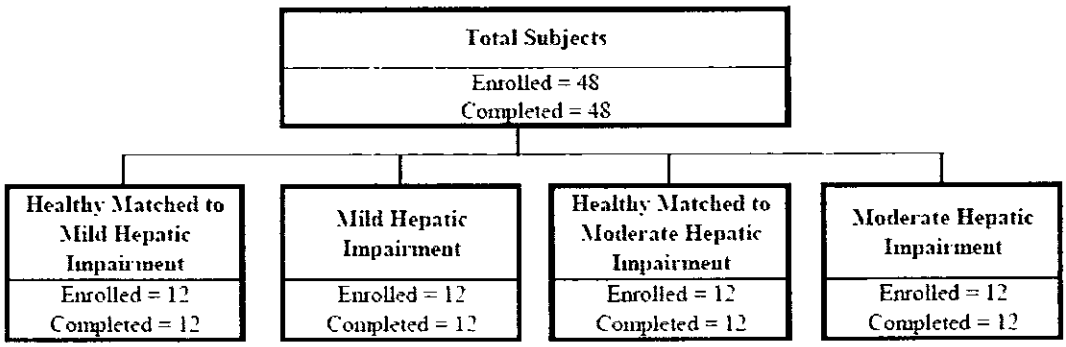
The concentrations of ramelteon and its metabolites in human urine were measured by [ ] validated concentration range of [ ] ng/mL for ramelteon and [ ] ng/mL for its metabolites. Concentrations below the lower limit of quantification were set to 0 for pharmacokinetic analysis.

Criteria for Evaluation:
Pharmacokinetic:
The following serum and urine pharmacokinetic parameters were calculated for ramelteon and its metabolites on Day 1: area under concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-tlqc]), area under concentration-time curve from 0 to 48 hours (AUC[0-48]), area under concentration-time curve from 0 to infinity (AUC[0-inf]), maximum observed concentration (Cmax), time at which maximum concentration is observed (Tmax), terminal elimination rate constant (λz), terminal half-life (T1/2), amount excreted in urine (XU) over 48 hours postdose (XU[0-48]), renal clearance (CLr), and apparent oral clearance corrected for bioavailability (CL/F) (for unchanged ramelteon only). For M-II and M-III, XU(0-48) were evaluated for the unconjugated and total forms. The following serum and urine pharmacokinetic parameters were calculated for ramelteon and its metabolites on Day 8: AUC(0-τ), Cmax, minimum observed concentration (Cmin), Tmax, λz, T1/2, XU(0-τ), CLr, and CL/F (for unchanged ramelteon only). For M-II and M-III, XU(0-τ) was evaluated for the unconjugated and total forms.

Safety:
Safety variables included adverse events, clinical laboratory test results, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

Statistical Methods
Pharmacokinetic Measures:
A 2 sample t-test was performed on AUC(0-tlqc), AUC(0-inf), Cmax, and λz for single dose, and AUC(0-t), Cmax, λz for multiple doses to compare the hepatically impaired subject (mild and moderate) group to the corresponding matched normal subject group. The 90% confidence intervals of the mean ratios for subjects with hepatic impairment versus normal subjects (eg, AUC(0-tlqc) for subjects with mild hepatic impairment/AUC(0-tlqc) for their matched controls) were provided.
The Kruskal-Wallis test was performed on Tmax for both single and multiple doses to compare the hepatically impaired subject (mild or moderate) group to the corresponding matched normal subject group.

SUMMARY OF RESULTS
Subject Disposition:
Forty-eight subjects (mean age of 54.1 years), including 32 men and 16 women, were enrolled in the study. All enrolled subjects completed the study.



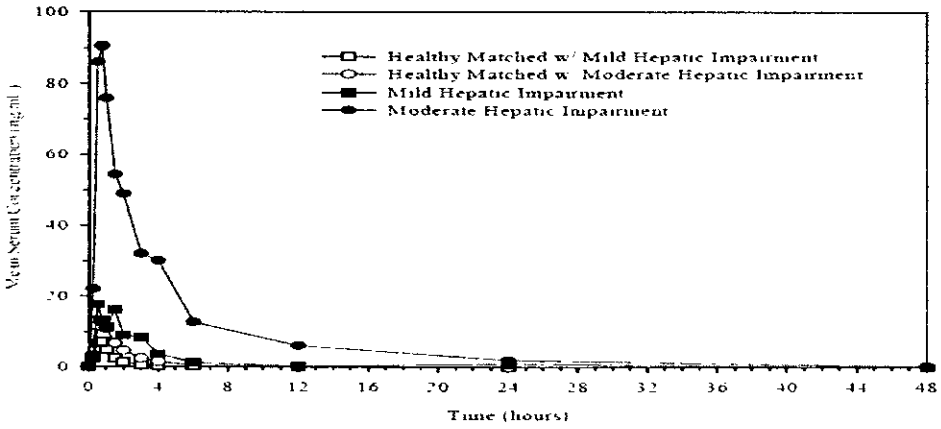
Summary of Demographic and Baseline Characteristics for All Subjects

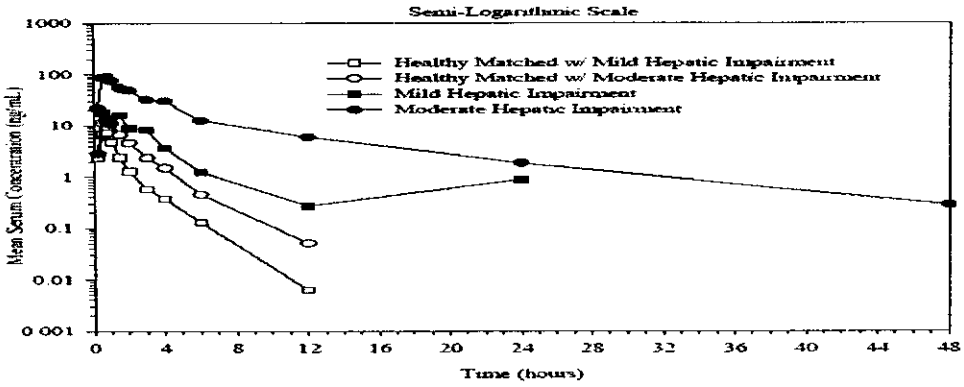
Characteristic	Statistics	Treatment Group				Overall
		Healthy Matched to Mild Hepatic Impairment	Mild Hepatic Hepatic Impairment	Healthy Matched to Moderate Impairment	Moderate Hepatic Impairment	
Age (years)	N	12	12	12	12	48
	Mean	54.2	56.6	52.5	53.1	54.1
	SD	9.86	9.19	10.12	7.17	9.00
Gender						
Male	N (%)	8 (66.7)	8 (66.7)	8 (66.7)	8 (66.7)	32 (66.7)
Female	N (%)	4 (33.3)	4 (33.3)	4 (33.3)	4 (33.3)	16 (33.3)
Race						
Caucasian	N (%)	8 (66.7)	8 (66.7)	4 (33.3)	5(41.7)	25 (52.1)
Hispanic	N (%)	4 (33.3)	4 (33.3)	8 (66.7)	7 (58.3)	23 (47.9)
Weight (kg)	Mean	81.35	82.63	74.16	82.14	80.07
	SD	13.681	14.955	11.347	14.262	13.638
Height (cm)	Mean	174.41	170.60	167.64	170.18	170.71
	SD	9.887	10.322	7.959	9.442	9.460
BMI (kg/m2)	Mean	26.638	28.421	26.247	28.044	27.337
	SD	2.9977	5.3806	2.3478	3.8355	3.8037

Effect of Hepatic Impairment on Ramelteon and Metabolites on Day 1

The Day 1 serum and urine pharmacokinetics of ramelteon, its major metabolite M-II, and minor metabolites M-I, M-III, and M-IV were assessed following a single oral dose of ramelteon to subjects with mild and moderate hepatic impairment and to corresponding healthy matched controls.

Mean Serum Concentration of Ramelteon on Day 1





Serum and Urine Pharmacokinetic Parameter Results for Ramelteon on Day 1

Comparison	Parameter	N	Arithmetic Mean (SD) Healthy (a) (R)	N	Hepatic Impaired (b) (T)
Mild to Healthy	Cmax (ng/mL)	12	9.01 (11.775)	12	32.7 (25.34)
	AUC(0-tlqc) (ng·hr/mL)	12	9.43 (11.527)	12	53.1 (51.39)
	AUC(0-inf) (ng·hr/mL)	11	10.6 (11.88)	10	42.9 (33.34)
	T1/2 (hr)	11	1.48 (0.426)	10	1.65 (0.514)
	Tmax (hr) (c)	12	0.508 (0.250, 1.50)	12	0.500 (0.500, 3.00)
	XU(0-48) (mg)	12	0.0000809 (0.00019058)	12	0.000377 (0.0006133)
	CL/F (L/hr)	11	3278 (2894.1)	10	2355 (5025.4)
	CLr (mL/min)	12	0.0585 (0.15857)	12	0.0822 (0.11873)
Moderate to Healthy	Cmax (ng/mL)	12	16.4 (14.21)	12	117 (108.1)
	AUC(0-tlqc) (ng·hr/mL)	12	23.8 (26.43)	12	360 (479.1)
	AUC(0-inf) (ng·hr/mL)	12	24.2 (26.70)	11	295 (441.9)
	T1/2 (hr)	12	1.34 (0.351)	11	3.35 (2.518)
	Tmax (hr) (c)	12	0.625 (0.250, 1.00)	12	0.750 (0.500, 1.50)
	XU(0-48) (mg)	12	0.000413 (0.0007936)	12	0.00463 (0.007571)
	CL/F (L/hr)	12	2103 (2249.5)	11	391 (563.8)
	CLr (mL/min)	12	0.138 (0.2660)	12	0.149 (0.1783)

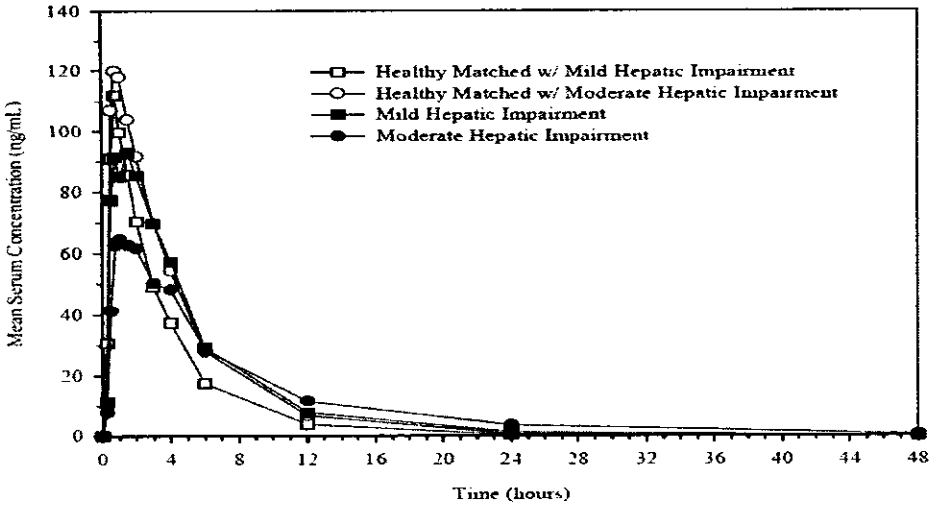
Comparison Results for Ramelteon on Day 1

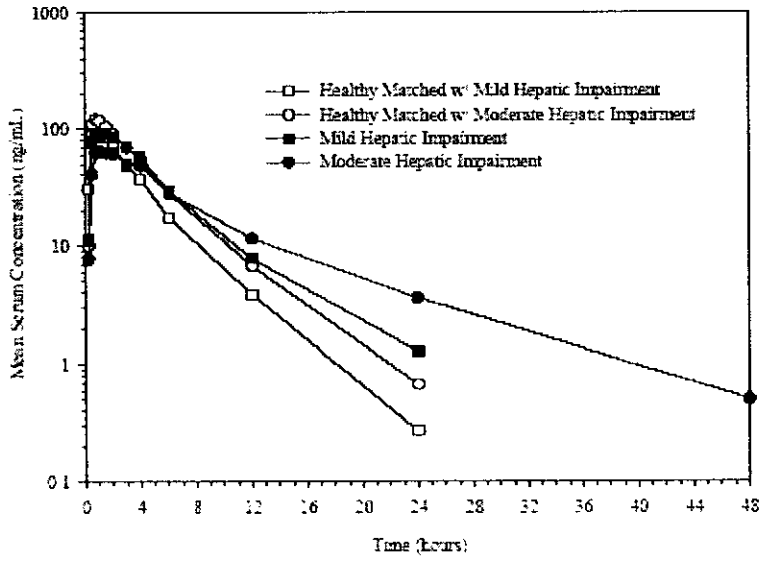
Comparison	Parameter	Least Squares Means Healthy (a) (R)	Hepatic Impaired (b) (T)	Mean Ratio (%) (100_T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	4.43	21.1	476.14	(186.83, 1213.44)	0.0090
	AUC(0-tlqc) (ng·hr/mL)	5.02	28.6	569.58	(212.79, 1524.60)	0.0061
	AUC(0-inf) (ng·hr/mL)	6.99	24.2	346.34	(138.07, 868.78)	0.0306
Moderate to Healthy	Cmax (ng/mL)	10.7	60.9	570.38	(237.99, 1367.02)	0.0024
	AUC(0-tlqc) (ng·hr/mL)	13.2	130	987.61	(357.89, 2725.32)	0.0008
	AUC(0-inf) (ng·hr/mL)	13.6	109	797.40	(295.02, 2155.30)	0.0017

There was significantly higher exposure of ramelteon in mildly and moderately hepatically impaired subjects compared to the healthy matched controls on Day 1. The moderately impaired group had larger increases in exposure relative to the healthy matched controls. Urinary excretion of unchanged ramelteon was minimal and did not appear different in the hepatically impaired subjects compared to the corresponding healthy control groups.

Serum and Urine M-II Results

Mean Serum Concentration of M-II on Day 1





Serum and Urine Pharmacokinetic Parameter Results for M-II on Day 1

Comparison	Parameter	N	Arithmetic Mean (SD) Healthy (a) (R)	N	Hepatic Impaired (b) (T)
Mild to Healthy	Cmax (ng/mL)	12	126 (37.2)	12	134 (65.4)
	AUC(0-tlqc) (ng·hr/mL)	12	391 (149.3)	12	529 (204.0)
	AUC(0-inf) (ng·hr/mL)	12	398 (150.5)	12	543 (215.9)
	T1/2 (hr)	12	2.54 (0.823)	12	3.17 (1.149)
	Tmax (hr) (c)	12	0.750 (0.250, 1.50)	12	1.00 (0.500, 4.00)
	XU(0-48) (mg) (d)	12	0.0244 (0.01259)	12	0.0188 (0.01049)
	XU(0-48) (mg) (e)	12	0.720 (0.1573)	12	0.846 (0.1888)
	CLr (mL/min)	12	1.09 (0.685)	12	0.591 (0.2945)
Moderate to Healthy	Cmax (ng/mL)	12	153 (61.9)	12	86.8 (47.04)
	AUC(0-tlqc) (ng·hr/mL)	12	545 (231.9)	12	523 (172.2)
	AUC(0-inf) (ng·hr/mL)	12	552 (234.1)	12	541 (182.5)
	T1/2 (hr)	12	2.89 (0.827)	12	5.58 (4.122)
	Tmax (hr) (c)	12	0.750 (0.500, 2.00)	12	1.50 (0.500, 4.00)
	XU(0-48) (mg) (d)	12	0.0274 (0.02017)	12	0.0212 (0.00975)
	XU(0-48) (mg) (e)	12	0.789 (0.2868)	12	0.830 (0.3341)
	CLr (mL/min)	12	0.911 (0.7150)	12	0.703 (0.3661)

Comparison Results for M-II on Day 1

Comparison	Parameter	Least Squares Means Healthy (a) (R)	Hepatic Impaired (b) (T)	Mean Ratio (%) (100_T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	120	124	103.40	(80.55, 132.74)	0.8202
	AUC(0-tlqc) (ng·hr/mL)	364	497	136.47	(104.15, 178.83)	0.0609
	AUC(0-inf) (ng·hr/mL)	371	509	137.12	(104.47, 179.97)	0.0588
Moderate to Healthy	Cmax (ng/mL)	142	73.5	51.73	(35.65, 75.06)	0.0060
	AUC(0-tlqc) (ng·hr/mL)	501	498	99.56	(76.23, 130.03)	0.9775
	AUC(0-inf) (ng·hr/mL)	508	515	101.43	(77.57, 132.61)	0.9286

There was 36 to 37% higher exposure of M-II in mildly hepatically impaired subjects relative to the healthy matched controls on Day 1, but the increase was not statistically significant. The moderately impaired group had only 1% higher exposure to M-II relative to the healthy matched controls (p ε0.9286). Urinary excretion of unconjugated and total M-II was low and did not appear to be different in the hepatically impaired subjects as compared to the corresponding healthy matched controls. Median urinary excretion of unconjugated M-II comprised only 2 to 4% of total M-II in urine among subject groups.

Metabolites I, III, and IV:

Table 11.e Comparison Results for M-I, M-III, and M-IV on Day 1

Analyte	Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
M-I	Mild to Healthy	Cmax (ng/mL)	6.48	5.33	82.27	(57.97, 116.77)	0.3490
		AUC(0-tlqc) (ng·hr/mL)	7.68	8.07	105.01	(75.56, 145.94)	0.8011
		AUC(0-inf) (ng·hr/mL)	9.19	9.16	99.74	(72.47, 137.28)	0.9891
	Moderate to Healthy	Cmax (ng/mL)	8.41	5.25	62.37	(43.56, 89.31)	0.0342
		AUC(0-tlqc) (ng·hr/mL)	10.2	11.4	112.03	(80.07, 156.73)	0.5673
		AUC(0-inf) (ng·hr/mL)	11.0	13.2	119.39	(83.53, 170.65)	0.4028
M-III	Mild to Healthy	Cmax (ng/mL)	0.552	2.42	438.20	(97.23, 1975.00)	0.1061
		AUC(0-tlqc) (ng·hr/mL)	0.565	3.68	651.15	(126.58, 3349.60)	0.0623
		AUC(0-inf) (ng·hr/mL)	4.28	7.49	174.98	(112.83, 271.36)	0.0452
	Moderate to Healthy	Cmax (ng/mL)	2.59	3.07	118.84	(78.97, 178.85)	0.4760
		AUC(0-tlqc) (ng·hr/mL)	3.56	11.1	312.56	(140.51, 695.28)	0.0228
		AUC(0-inf) (ng·hr/mL)	6.78	22.8	336.52	(122.50, 924.42)	0.0540
M-IV	Mild to Healthy	Cmax (ng/mL)	11.2	11.6	103.46	(82.18, 130.25)	0.8022
		AUC(0-tlqc) (ng·hr/mL)	58.5	85.0	145.36	(104.95, 201.33)	0.0613
		AUC(0-inf) (ng·hr/mL)	64.7	94.7	146.37	(104.57, 204.86)	0.0646
	Moderate to Healthy	Cmax (ng/mL)	11.4	6.37	55.80	(42.19, 73.80)	0.0017
		AUC(0-tlqc) (ng·hr/mL)	69.3	68.1	98.25	(69.62, 138.66)	0.9307
		AUC(0-inf) (ng·hr/mL)	77.0	77.9	101.16	(71.58, 142.95)	0.9548

Source: Tables 14.2.1.7 and 14.2.1.8.
R indicates Reference, T. Test. CI. Confidence Interval
(a) Healthy subjects matched with subjects with mild or moderate hepatic impairment.
(b) Subjects with mild or moderate hepatic impairment.

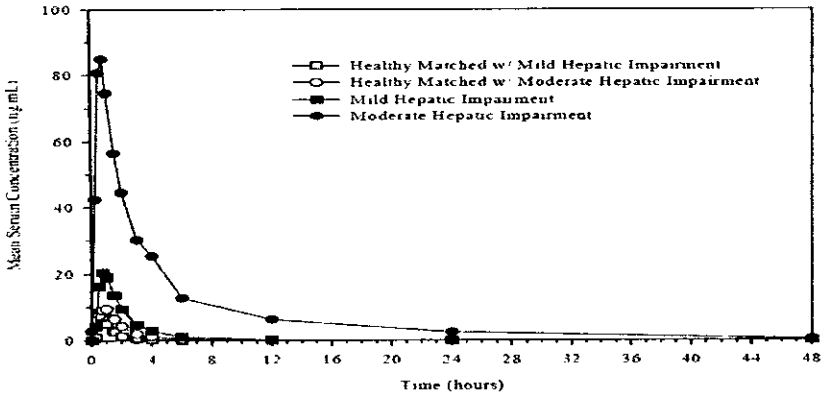
There was significantly higher exposure to M-III and marginal increases in exposure to M-I and M-IV in hepatically impaired subjects compared to the healthy matched controls on Day 1. Urinary excretion of M-I and M-IV was minimal and did not appear to be different in the hepatically impaired subjects compared to the corresponding healthy matched controls. Urinary excretion of total and unconjugated M-III was also very low. Median unconjugated M-III was undetectable in healthy and mildly impaired groups, but comprised 12% of total M-III in urine of moderate impaired subjects on Day 1.

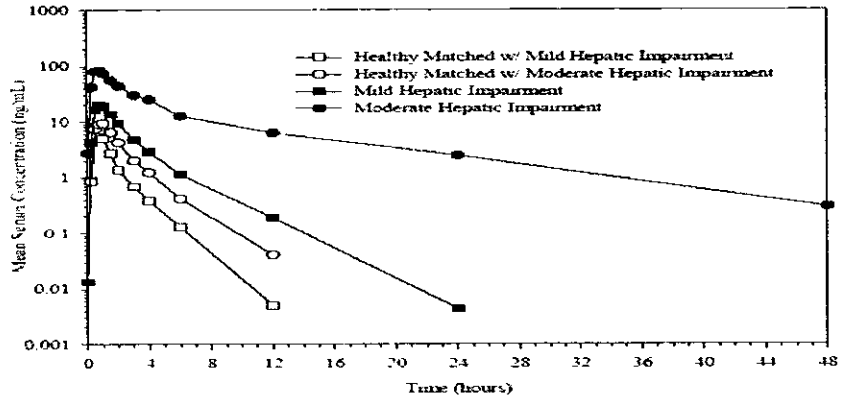
Effect of Hepatic Impairment on Ramelteon and Metabolites on Day 8

The Day 8 serum pharmacokinetics of ramelteon, its major metabolite M-II, and metabolites M-I, M-III, and M-IV were assessed after multiple dose administration of ramelteon to mildly and moderately hepatically impaired subjects and corresponding healthy matched controls.

Serum and Urine Ramelteon

Mean Serum Concentration of Ramelteon on Day 8





Serum and Urine Pharmacokinetic Parameter Results for Ramelteon on Day 8

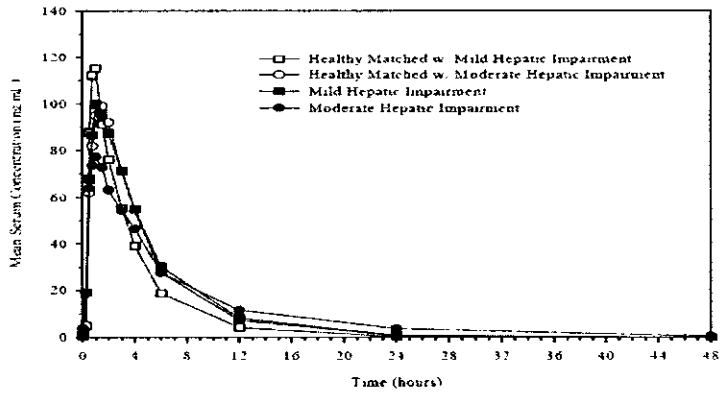
Comparison	Parameter	N	Arithmetic Mean (SD) Healthy (a) (R) N	Hepatic Impaired (b) (T)
Mild to Healthy	Cmax (ng/mL)	12	9.57 (10.323) 12	24.6 (19.41)
	AUC(0-τ) (ng·hr/mL)	12	10.3 (11.71) 12	46.7 (41.54)
	Cmin (ng/mL)	12	0 (0) 12	0.00442 (0.015300)
	T1/2 (hr)	12	1.18 (0.303) 12	1.77 (0.641)
	Tmax (hr) (c)	12	0.625 (0.500, 1.00) 12	0.750 (0.500, 1.50)
	XU(0-τ) (mg)	12	0.000127 (0.0002334) 12	0.000512 (0.0009379)
	CL/F (L/hr)	12	6689 (12933.9) 12	3909 (7531.9)
	CLr (mL/min)	12	0.347 (1.0177) 12	0.0957 (0.13428)
Moderate to Healthy	Cmax (ng/mL)	12	11.8 (11.96) 12	105 (104.9)
	AUC(0-τ) (ng·hr/mL)	12	20.3 (25.91) 12	333 (446.0)
	Cmin (ng/mL)	12	0 (0) 12	2.24 (4.005)
	T1/2 (hr)	12	1.28 (0.334) 12	3.85 (2.836)
	Tmax (hr) (c)	12	1.00 (0.500, 1.50) 12	0.633 (0.250, 1.00)
	XU(0-τ) (mg)	12	0.000288 (0.0006810) 12	0.00540 (0.009334)
	CL/F (L/hr)	12	2196 (2231.6) 12	348 (579.4)
	CLr (mL/min)	12	0.0810 (0.19879) 12	0.243 (0.1990)

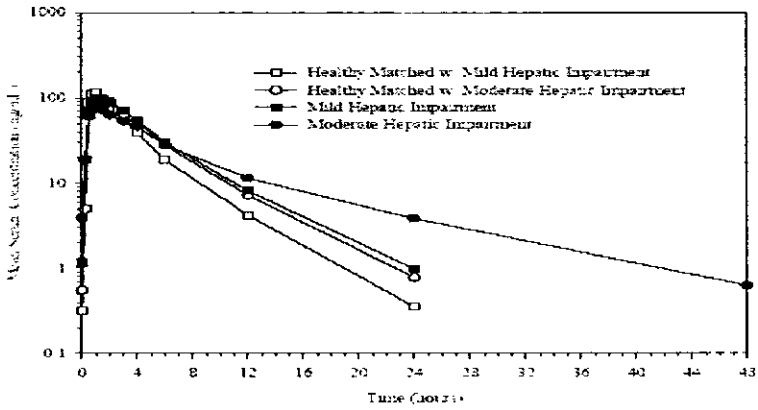
Comparison	Parameter	Least Squares Means		Mean Ratio (%) (100_T/R)	90% CI of Ratio (%)	P-value
		Healthy (a) (R)	Hepatic Impaired (b) (T)			
Mild to Healthy	Cmax (ng/mL)	5.20	12.8	246.17	(88.19, 687.15)	0.1460
	AUC(0-τ) (ng·hr/mL)	5.79	20.7	358.16	(121.91, 1052.28)	0.0543
Moderate to Healthy	Cmax (ng/mL)	7.37	61.7	837.03	(379.45, 1846.43)	0.0001
	AUC(0-τ) (ng·hr/mL)	11.7	125	1067.25	(415.62, 2740.53)	0.0003

Similar to the Day 1 results, there was higher exposure of ramelteon in mildly and moderately hepatically impaired subjects relative to the healthy matched controls on Day 8 (p=0.0543 and p=0.0003, respectively). The moderately impaired group had larger increases in exposure relative to the healthy matched controls, which in part was attributed to 3 moderately impaired subjects who had at least 4-fold higher ramelteon exposure than the other 9 moderately impaired subjects. The 3 moderately impaired subjects with the highest ramelteon exposure had the highest Child-Pugh scores (9 versus 7 or 8 in other moderate impaired subjects). Urinary excretion of unchanged ramelteon was low in both the hepatically impaired subject groups and their corresponding healthy controls.

Serum and Urine M-II

Mean Serum Concentration of M-II on Day 8





Serum and Urine Pharmacokinetic Parameter Results for M-II on Day 8

Comparison	Parameter	N	Arithmetic Mean (SD)	
			Healthy (a) (R) N	Hepatic Impaired (b) (T)
Mild to Healthy	Cmax (ng/mL)	12	128 (31.0) 12	124 (42.7)
	AUC(0-τ) (ng·hr/mL)	12	426 (146.0) 12	548 (184.6)
	Cmin (ng/mL)	12	0.295 (0.4752) 12	0.883 (1.0514)
	T1/2 (hr)	12	2.79 (0.860) 12	3.28 (0.812)
	Tmax (hr) (c)	12	0.875 (0.500, 1.00) 12	1.00 (0.500, 3.00)
	XU(0-τ) (mg) (d)	12	0.0295 (0.01784) 12	0.0244 (0.01314)
	XU(0-τ) (mg) (e)	12	0.818 (0.1898) 12	0.778 (0.2032)
	CLr (mL/min)	12	1.42 (1.361) 12	0.801 (0.4992)
Moderate to Healthy	Cmax (ng/mL)	12	111 (34.5) 12	86.9 (33.10)
	AUC(0-τ) (ng·hr/mL)	12	524 (234.8) 12	514 (136.2)
	Cmin (ng/mL)	12	0.556 (0.9117) 12	3.20 (4.483)
	T1/2 (hr)	12	2.99 (0.842) 12	6.39 (5.512)
	Tmax (hr) (c)	12	1.50 (0.750, 2.00) 12	1.00 (0.500, 4.00)
	XU(0-τ) (mg) (d)	12	0.0286 (0.02459) 12	0.0259 (0.01718)
	XU(0-τ) (mg) (e)	12	0.859 (0.2581) 12	0.836 (0.3203)
	CLr (mL/min)	12	0.971 (0.8768) 12	0.832 (0.5953)

Comparison Results for M-II on Day 8

Table 11.i Comparison Results for M-II on Day 8

Comparison	Parameter	Least Squares Means		Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
		Healthy (a) (R)	Hepatic Impaired (b) (T)			
Mild to Healthy	Cmax (ng/mL)	124	117	94.28	(75.15, 118.27)	0.6598
	AUC(0-τ) (ng·hr/mL)	401	519	129.32	(100.03, 167.19)	0.0996
Moderate to Healthy	Cmax (ng/mL)	107	80.5	75.48	(58.04, 98.17)	0.0796
	AUC(0-τ) (ng·hr/mL)	483	496	102.73	(79.82, 132.22)	0.8560

Source: Tables 14.2.1.15 and 14.2.1.16.
R indicates Reference; T, Test; CI, Confidence Interval.
(a) Healthy subjects matched with subjects with mild or moderate hepatic impairment.
(b) Subjects with mild or moderate hepatic impairment.

Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Mild to Healthy	Cmax (ng/mL)	124	117	94.28	(75.15, 118.27)	0.6598
	AUC(0-τ) (ng·hr/mL)	401	519	129.32	(100.03, 167.19)	0.0996
Moderate to Healthy	Cmax (ng/mL)	107	80.5	75.48	(58.04, 98.17)	0.0796
	AUC(0-τ) (ng·hr/mL)	483	496	102.73	(79.82, 132.22)	0.8560

Similar to the Day 1 results, there was marginally (29%) higher exposure to M-II in mildly hepatically impaired subjects compared to the healthy matched controls on Day 8. Moderately impaired subjects had only a 3% increase in exposure to M-II compared to the healthy matched controls. Urinary excretion of unconjugated and total M-II was minimal and did not appear different in the hepatically impaired subjects compared to the corresponding healthy matched controls. Similar to Day 1 results, median urinary excretion of unconjugated M-II comprised only 3% to 4% of total M-II in urine.

A summary of least squares mean pharmacokinetic results for M-I, M-III, and M-IV on Day 8 are presented in Table 11.j. The corresponding arithmetic mean summary results are listed in Section 14.2.

Table 11.j Comparison Results for M-I, M-III, and M-IV on Day 8

Analyte	Comparison	Parameter	Least Squares Means: Healthy (a) (R)	Least Squares Means: Hepatic Impaired (b) (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
M-I	Mild to Healthy	Cmax (ng/mL)	7.73	6.39	82.66	(62.78, 108.84)	0.2474
		AUC(0-τ) (ng·hr/mL)	8.96	9.43	105.21	(74.58, 148.41)	0.8023
	Moderate to Healthy	Cmax (ng/mL)	7.46	6.22	83.32	(61.87, 112.22)	0.3041
		AUC(0-τ) (ng·hr/mL)	11.2	12.8	114.07	(84.92, 153.22)	0.4518
M-III	Mild to Healthy	Cmax (ng/mL)	0.950	1.28	134.61	(27.35, 662.60)	0.7518
		AUC(0-τ) (ng·hr/mL)	1.24	2.25	181.31	(30.44, 1080.07)	0.5727
	Moderate to Healthy	Cmax (ng/mL)	1.80	3.67	203.80	(139.10, 298.59)	0.0041
		AUC(0-τ) (ng·hr/mL)	3.28	14.9	455.13	(214.05, 967.75)	0.0023
M-IV	Mild to Healthy	Cmax (ng/mL)	12.0	12.1	100.81	(81.90, 124.09)	0.9473
		AUC(0-τ) (ng·hr/mL)	71.6	97.1	135.71	(99.54, 185.02)	0.1049
	Moderate to Healthy	Cmax (ng/mL)	10.4	7.34	70.92	(54.51, 92.27)	0.0354
		AUC(0-τ) (ng·hr/mL)	77.5	78.3	101.01	(73.93, 138.03)	0.9563

Source: Tables 14.2.1.15 and 14.2.1.16
R indicates Reference, T, Test: CI. Confidence Interval
(a) Healthy subjects matched with subjects with mild or moderate hepatic impairment
(b) Subjects with mild or moderate hepatic impairment

Similar to the Day 1 results, there was higher exposure to metabolite M-III and no statistically significant differences in M-I and M-IV AUC in hepatically impaired subjects compared to the healthy matched controls on Day 8. Urinary excretion of M-I and M-IV was minimal and did not appear different in the hepatically impaired subjects

Pharmacokinetic Results:
Single and multiple dose pharmacokinetic parameters for ramelteon and its metabolites were evaluated in serum and urine on Day 1 and Day 8 in hepatically impaired subjects and in healthy matched controls. Examination of predose level results suggests that steady state was achieved for ramelteon and its metabolites by the morning of Day 5 (after 2 days of multiple once daily dosing) in all the subject groups. Statistical results for comparisons between groups are summarized in the following sections. In the majority of hepatic subjects, there was poor correlation between degree of hepatic impairment (as determined by Child-Pugh score) and increase in ramelteon exposure. The exceptions were 3 moderately impaired subjects with the highest Child-Pugh scores (9), who had at least 4-fold higher ramelteon exposure than the other impaired subjects with Child-Pugh scores ranging between 5 and 8.

Serum Pharmacokinetics: Day 1 Results
Statistical results for mild hepatically impaired subjects compared to healthy matched controls on Day 1 are presented in the following table.

		Least Squares Means				
Analyte	Parameter	Healthy Matched Control (R)	Mild Hepatic Impairment (T)	Mean Ratio (%) (100*T/R)	90% CI of Ratio (%)	P-value
Ramelteon	Cmax (ng/mL)	4.43	21.1	476.14	(186.83, 1213.44)	0.0090
	AUC(0-tlqc) (ng·hr/mL)	5.02	28.6	569.58	(212.79, 1524.60)	0.0061
	AUC(0-inf) (ng·hr/mL)	6.99	24.2	346.34	(138.07, 868.78)	0.0306
M-I	Cmax (ng/mL)	6.48	5.33	82.27	(57.97, 116.77)	0.3490
	AUC(0-tlqc) (ng·hr/mL)	7.68	8.07	105.01	(75.56, 145.94)	0.8011
	AUC(0-inf) (ng·hr/mL)	9.19	9.16	99.74	(72.47, 137.28)	0.9891
M-II	Cmax (ng/mL)	120	124	103.40	(80.55, 132.74)	0.8202
	AUC(0-tlqc) (ng·hr/mL)	364	497	136.47	(104.15, 178.83)	0.0609
	AUC(0-inf) (ng·hr/mL)	371	509	137.12	(104.47, 179.97)	0.0588
M-III	Cmax (ng/mL)	0.552	2.42	438.20	(97.23, 1975.00)	0.1061
	AUC(0-tlqc) (ng·hr/mL)	0.565	3.68	651.15	(126.58, 3349.60)	0.0623
	AUC(0-inf) (ng·hr/mL)	4.28	7.49	174.98	(112.83, 271.36)	0.0452
M-IV	Cmax (ng/mL)	11.2	11.6	103.46	(82.18, 130.25)	0.8022
	AUC(0-tlqc) (ng·hr/mL)	58.5	85.0	145.36	(104.95, 201.33)	0.0613
	AUC(0-inf) (ng·hr/mL)	64.7	94.7	146.37	(104.57, 204.86)	0.0646

Source: Table 14.2.1.7.
R indicates Reference; T, Test; CI, Confidence Interval.

There were statistically significantly higher exposures to ramelteon and M-III in mildly hepatically impaired subjects relative to the healthy matched controls on Day 1.

Statistical results for moderately hepatically impaired subjects compared to healthy matched controls on Day 1 are presented in the following table.

Analyte	Parameter	Least Squares Means: Healthy Matched Control (R)	Least Squares Means: Moderate Hepatic Impairment (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Ramelteon	Cmax (ng/mL)	10.7	60.9	570.38	(237.99, 1367.02)	0.0024
	AUC(0-tlqc) (ng·hr/mL)	13.2	130	987.61	(357.89, 2725.32)	0.0008
	AUC(0-inf) (ng·hr/mL)	13.6	109	797.40	(295.02, 2155.30)	0.0017
M-I	Cmax (ng/mL)	8.41	5.25	62.37	(43.56, 89.31)	0.0342
	AUC(0-tlqc) (ng·hr/mL)	10.2	11.4	112.03	(80.07, 156.73)	0.5673
	AUC(0-inf) (ng·hr/mL)	11.0	13.2	119.39	(83.53, 170.65)	0.4028
M-II	Cmax (ng/mL)	142	73.5	51.73	(35.65, 75.06)	0.0060
	AUC(0-tlqc) (ng·hr/mL)	501	498	99.56	(76.23, 130.03)	0.9775
	AUC(0-inf) (ng·hr/mL)	508	515	101.43	(77.57, 132.61)	0.9286
M-III	Cmax (ng/mL)	2.59	3.07	118.84	(78.97, 178.85)	0.4760
	AUC(0-tlqc) (ng·hr/mL)	3.56	11.1	312.56	(140.51, 695.28)	0.0228
	AUC(0-inf) (ng·hr/mL)	6.78	22.8	336.52	(122.50, 924.42)	0.0540
M-IV	Cmax (ng/mL)	11.4	6.37	55.80	(42.19, 73.80)	0.0017
	AUC(0-tlqc) (ng·hr/mL)	69.3	68.1	98.25	(69.62, 138.66)	0.9307
	AUC(0-inf) (ng·hr/mL)	77.0	77.9	101.16	(71.58, 142.95)	0.9548

Source: Table 14.2.1.8.
R indicates Reference; T, Test; CI, Confidence Interval

There was statistically significantly higher exposure of ramelteon and M-III in moderately hepatically impaired subjects relative to the healthy matched controls on Day 1. After a single 16 mg dose of ramelteon, the increases in least squares mean AUCs of M-II (major metabolite of ramelteon) were greater in mildly hepatically impaired subjects (36% to 37% compared to healthy matched controls) than in moderately hepatically impaired subjects (about 1% compared to healthy matched controls).

Serum Pharmacokinetics: Day 8 Results

Statistical results for mildly hepatically impaired subjects compared to healthy matched controls on Day 8 are presented in the following table.

Analyte	Parameter	Least Squares Means: Healthy Matched Control (R)	Least Squares Means: Mild Hepatic Impairment (T)	Mean Ratio (%) (100•T/R)	90% CI of Ratio (%)	P-value
Ramelteon	Cmax (ng/mL)	5.20	12.8	246.17	(88.19, 687.15)	0.1460
	AUC(0-τ) (ng·hr/mL)	5.79	20.7	358.16	(121.91, 1052.28)	0.0543
M-I	Cmax (ng/mL)	7.73	6.39	82.66	(62.78, 108.84)	0.2474
	AUC(0-τ) (ng·hr/mL)	8.96	9.43	105.21	(74.58, 148.41)	0.8023
M-II	Cmax (ng/mL)	124	117	94.28	(75.15, 118.27)	0.6598
	AUC(0-τ) (ng·hr/mL)	401	519	129.32	(100.03, 167.19)	0.0996
M-III	Cmax (ng/mL)	0.950	1.28	134.61	(27.35, 662.60)	0.7518
	AUC(0-τ) (ng·hr/mL)	1.24	2.25	181.31	(30.44, 1080.07)	0.5727
M-IV	Cmax (ng/mL)	12.0	12.1	100.81	(81.90, 124.09)	0.9473
	AUC(0-τ) (ng·hr/mL)	71.6	97.1	135.71	(99.54, 185.02)	0.1049

Source: Table 14.2.1.15.
R indicates Reference, T, Test, CI, Confidence Interval.

There was higher exposure to ramelteon and M-III in mildly hepatically impaired subjects relative to the healthy matched controls on Day 8, but the increases were not statistically significant.
Statistical results for moderately hepatically impaired subjects compared to healthy matched controls on Day 8 are presented in the following table.

Analyte	Parameter	Least Squares Means: Healthy Matched Control (R)	Least Squares Means: Moderate Hepatic Impairment (T)	Mean Ratio (%) (100*T/R)	90% CI of Ratio (%)	P-value
Ramelteon	Cmax (ng/mL)	7.37	61.7	837.03	(379.45, 1846.43)	0.0001
	AUC(0-τ) (ng·hr/mL)	11.7	125	1067.25	(415.62, 2740.53)	0.0003
M-I	Cmax (ng/mL)	7.46	6.22	83.32	(61.87, 112.22)	0.3041
	AUC(0-τ) (ng·hr/mL)	11.2	12.8	114.07	(84.92, 153.22)	0.4518
M-II	Cmax (ng/mL)	107	80.5	75.48	(58.04, 98.17)	0.0796
	AUC(0-τ) (ng·hr/mL)	483	496	102.73	(79.82, 132.22)	0.8560
M-III	Cmax (ng/mL)	1.80	3.67	203.80	(139.10, 298.59)	0.0041
	AUC(0-τ) (ng·hr/mL)	3.28	14.9	455.13	(214.05, 967.75)	0.0023
M-IV	Cmax (ng/mL)	10.4	7.34	70.92	(54.51, 92.27)	0.0354
	AUC(0-τ) (ng·hr/mL)	77.5	78.3	101.01	(73.93, 138.03)	0.9563

Source: Table 14.2.1.16.
R indicates Reference; T, Test; CI, Confidence Interval.

Similar to the Day 1 results, there was statistically significantly higher exposure to ramelteon and M-III in moderately hepatically impaired subjects compared to the healthy matched controls on Day 8. The increases in least squares mean steady-state AUC of M-II was greater in mildly impaired subjects (29% compared to healthy matched controls) than in moderately impaired subjects (3% compared to healthy matched controls).

Urine Pharmacokinetics: Day 1 and Day 8 Results

Urinary excretion was minimal for ramelteon and its metabolites in all subject groups on Day 1 and Day 8. No trends or differences were noted in the urinary excretion data between the mildly and moderately hepatically impaired and corresponding healthy subject controls. Median urinary excretion of unconjugated M-II comprised only 2% to 4% of total M-II in urine among subject groups; whereas, the median unconjugated M-III in urine was undetectable in healthy and mildly impaired groups, but comprised 10% to 12% of median total M-III in urine in moderately impaired subjects.

Safety Results:
Thirty-eight of 48 subjects experienced at least 1 treatment emergent adverse event. Adverse events were mild in intensity except for 1 adverse event that was severe in intensity.

The incidence of all adverse events and treatment-related adverse events across treatment groups was 83.3% (10/12) for mildly hepatically impaired subjects compared to 75.0% (9/12) for their healthy matched controls and 75.0% (9/12) for moderately hepatically impaired subjects compared to 83.3% (10/12) for their healthy matched controls. The most commonly reported adverse event for each group was somnolence: 66.7% (8/12) for mildly hepatically impaired subjects compared to 50.0% (6/12) for their healthy matched controls and 58.3% (7/12) for moderately hepatically impaired subjects compared to 75.0% (9/12) for their healthy matched controls. The similar incidence of somnolence between healthy and hepatically impaired subjects suggests an apparent flat response between ramelteon exposure and effect.
No serious adverse events (SAEs) were reported, and no deaths occurred during the study.
No clinically meaningful changes in physical examination findings, ECG findings, or vital signs were reported in this study. Clinically significant laboratory values were reported for subjects with mild or moderate hepatic impairment; however, these values were considered consistent with disease and were not reported as adverse events.

Table 12.a All Adverse Events

System Organ Class Preferred Term (a)	Treatment Group Healthy Matched to Mild Hepatic Impairment N=12	Mild Hepatic Impairment N=12	Healthy Matched to Moderate Hepatic Impairment N=12	Moderate Hepatic Impairment N=12
Gastrointestinal Disorders				
Constipation	1 (8.3)	0 (0)	0 (0)	0 (0)
Flatulence	1 (8.3)	0 (0)	0 (0)	0 (0)
Loose Stools	0 (0)	0 (0)	0 (0)	1 (8.3)
Nausea	0 (0)	0 (0)	0 (0)	2 (16.7)
General Disorders and Administration Site Conditions				
Lethargy	1 (8.3)	0 (0)	1 (8.3)	3 (25.0)
Musculoskeletal and Connective Tissue Disorders				
Myalgia	1 (8.3)	0 (0)	0 (0)	0 (0)
Nervous Systems Disorders				
Dizziness	1 (8.3)	1 (8.3)	0 (0)	1 (8.3)
Headache NOS	2 (16.7)	2 (16.7)	2 (16.7)	2 (16.7)
Somnolence	6 (50.0)	8 (66.7)	9 (75.0)	7 (58.3)
Respiratory, Thoracic, and Mediastinal Disorders				
Nasal Congestion	0 (0)	1 (8.3)	0 (0)	1 (8.3)
Pharyngitis	0 (0)	1 (8.3)	0 (0)	1 (8.3)

Source: Table 14.3.1.2.
Parentheses indicate percentages of subjects.
(a) A subject who reported 2 or more adverse events within the same preferred term was counted only once for that term

CONCLUSIONS:

Single and multiple dose administration of 16 mg ramelteon resulted in significant increases in exposure to ramelteon in subjects with mild hepatic impairment (3.5 to 3.6-fold higher AUCs) and moderate hepatic impairment (8.0 to 10.7-fold higher AUCs) relative to their corresponding healthy matched controls.

In the majority of hepatic subjects, there was poor correlation between degree of hepatic dysfunction (Child-Pugh score) and increase in ramelteon exposure, except for 3 moderately impaired subjects with the highest Child-Pugh score (9) who had at least 4-fold higher ramelteon exposure than other impaired subjects.

The significant increases in exposure to the minor metabolite, M-III, in hepatically impaired subjects (1.7 to 1.8-fold in mild and 3.4 to 4.6-fold in moderate impairment) were not considered clinically important.

Exposures to major metabolite M-II, and to minor metabolites M-I and M-IV, were only marginally increased in mildly and moderately hepatically impaired subjects relative to the respective healthy matched controls.

Multiple doses of ramelteon 16 mg once daily for 5 days appeared to be safe and well tolerated when administered to subjects with mild to moderate hepatic impairment.

Subjects with severe hepatic impairment were not studied, thus use of ramelteon in such patients is not recommended.

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

4.5 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-782	Brand Name	[redacted]
OCPB Division (I, II, III)	II	Generic Name	Ramelteon (TAK-375)
Medical Division	HFD-170	Drug Class	Hypnotic
OCPB Reviewer	David Lee	Indication(s)	Insomnia
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Immediate release tablet
		Dosing Regimen	Single dose
Date of Submission	9/21/04	Route of Administration	Oral
Estimated Due Date of OCPB Review	-	Sponsor	Takeda, Inc
Medical Division Due Date	6/17/05	Priority Classification	1S
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	7	7	
Blood/plasma ratio:	x	2	2	
Plasma protein binding:	x	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3	3	
multiple dose:	X	3	3	
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:	X			

Subpopulation studies -				
ethnicity:	X	4	2	
gender:	X	2	2	
pediatrics:				Deferral
geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:				
Phase 1:				
Phase 2/3:	X	4	2	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS	X	2	2	
BCS class	X	2	2	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?

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/s/

David Lee
6/21/05 03:38:13 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/21/05 03:52:52 PM
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