

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-476

**Clinical Pharmacology and Biopharmaceutics
Review**

NOV 5 2004

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW**DRUG:** Estorra® (Eszopiclone)**PRIMARY REVIEWER:** Andre Jackson**NDA:** 21476**TYPE:** NDA**FORMULATION:** Oral Tablet**STRENGTH:** 1 mg**APPLICANT:** Sepracor Inc.

Submission Date: June 14, 2004

INDICATIONS: Insomnia**Generic Name:** Eszopiclone**REVIEW OF FIRM'S RESPONSE TO GENERAL CORRESPONDENCE****Background of 1.0 mg Dosage Strength**

The original NDA proposed Estorra™ 2.0 and 3.0 mg dosage strengths for commercialization. In addition, information for 1.0 mg dosage strength was also included in the original NDA in the Pharmaceutical Development Overview section (Section 4.A.3.4.4; cmc\product\product.pdf, page 13). As described in Section 4.A.3.4.4, the components of the 1.0 mg core tablets were the same as the 2.0 and 3.0 mg strengths, with a slight difference in the amount of active ingredient, which is quantitatively offset by an _____ to maintain a target core weight of _____ (i.e., less than SUPAC Level 1 change). In-process and release data from four batches were also provided. These batches were produced at the same scale as the registration batches for 2.0 and 3.0 mg (i.e., _____) and utilized _____ film coating. These batches have also been placed in ICH stability studies, utilizing a study plan essentially identical to the 2.0 and 3.0 mg studies.

The formulation and manufacturing process for the proposed commercial batches will be identical to the 1.0 mg development batches with the exception that a _____ film coating will be used for product differentiation purposes. Please note that this approach was discussed during the Pre-NDA CMC meeting on September 28, 2001. The Division agreed with Sepracor's plans to differentiate the additional dosage strength with a new color and stated that adding a new color to the coating of an immediate release formulation is usually not an issue (refer to FDA minutes issued March 6, 2002).

Based upon the requested formulation of this 1.0 mg strength and **that a formal waiver for this strength should be submitted to the FDA**, the following comments were sent to the firm.

FDA Comment 1:

1. The sponsor should submit a formal request to the FDA for waiver of the in vivo bioequivalence requirements for their proposed 1 mg tablet (see CFR 320.22(d)).

Firm's Reply:**Formal Request for Waiver**

As discussed in the May 4, 2004, End-of-Review Conference, a request for a waiver of the in vivo bioavailability requirements for the proposed commercial 1.0 mg eszopiclone product is provided in this submission, as an attachment to the cover letter (Cover Letter Attachment).

We believe that the 1.0 mg strength meets the conditions described in 21 CFR §320.22(d)(2)(ii) when compared with the 2.0 and 3.0 mg strengths. The 1.0 mg strength meets the same acceptance criteria, uses the same to-be-approved in vitro dissolution test method, and is proportionally similar in its active and inactive ingredients to the 2.0 mg and 3.0 mg strength tablets, as defined in CDER's *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations* (March 2003).

FDA Comment 2:

2. The sponsor should supply dissolution data for the new formulations using the following method which was used in the original NDA submission.

Summary of Drug Product Dissolution Method and Specification

Dosage Form	Esopiclone Tablets
Strengths	2.0 and 3.0 mg
Apparatus	USP Type 2 apparatus (paddle)
Media	—
Volume	—
Speed of Rotation	—
Acceptance Criterion	Q= — at 30 minutes

Firm's Reply:

2. Dissolution Data for 1.0 mg Product

In accordance with 21 CFR §320.22(d)(2)(ii), the 1.0 mg drug product meets an appropriate in vitro test namely, the same dissolution analytical method and acceptance criterion proposed for the 2.0 and 3.0 mg drug products and summarized in the Action Letter dated February 27, 2004. Dissolution data for the 1.0 mg strength are provided below as follows:

- Development tablets used in clinical studies, formulated with — coating of batches F0408001 (Table 1) and F0844001 (Table 2)
- Proposed commercial tablets, formulated with light blue coating of batches F1466001 (Table 3), F1469001 (Table 4), and F1477001 (Table 5). Analytical data show that each of these 1.0 mg batches meets the proposed dissolution acceptance criterion of Q = — at 30 minutes.

Please note: All dissolution Tables are in Appendix I.

FDA Comment 3:

3. The sponsor should consider scoring the 2 mg tablet as an alternative source for the proposed new 1 mg tablet.

Firm's Reply:

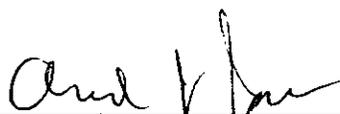
This comment was not sent to the firm in the Action letter.

Comment To the Firm:

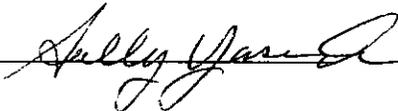
The 1 mg commercial Esopiclone tablet is compositionally proportional to the commercial 2 mg Esopiclone tablet which has been shown to be Bioequivalent to the 2 mg clinical Esopiclone tablet. Therefore the waiver of in vivo bioequivalence requirements for the 1 mg commercial Esopiclone tablet is granted.

SIGNATURES

Andre Jackson



RD/FT Initialed by Sally Yasuda, Pharm.D.
Acting Team Leader



Cc-NDA 21476, HFD-860(Jackson, Baweja, Rahman, Mehta, Yasuda), Central Documents
Room(Biopharm-CDR)
C:\Data\REVIEWS\ESZOPICLONE_NDA21476WAIVSEPR\Corres_res

APPENDIX I

Table 1. Dissolution Profiles for 1.0 mg — Drug Product Batch F0408001

Batch F0408001/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	80.8	88.8	94.9	98.0	100.4
RSD (%)	11.7	8.5	5.5	3.9	3.6

Table 2. Dissolution Profiles for 1.0 mg (—) Drug Product Batch F0844001

Batch F0844001/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	75.4	81.8	88.2	92.1	95.4
RSD (%)	11.8	8.7	6.2	5.3	4.4

Table 3. Dissolution Profiles for 1.0 mg (Light Blue) Drug Product Batch F1466001

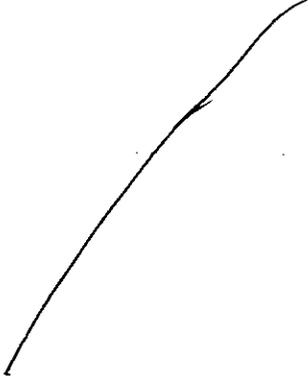
Batch F1466001/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	75.5	83.0	88.5	91.9	94.3
RSD (%)	6.4	5.0	4.3	3.8	3.6

Table 4. Dissolution Profiles for 1.0 mg (Light Blue) Drug Product Batch F1469001

Batch F1469001/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	74.1	82.7	89.6	93.1	94.8
RSD (%)	14.8	8.8	5.3	4.3	3.5

Table 5. Dissolution Profiles for 1.0 mg (Light Blue) Drug Product Batch F1477001

Batch F1477001/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	75.6	84.0	90.7	93.7	96.8
RSD (%)	9.9	6.0	3.5	2.7	2.6



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/s/

Andre Jackson
11/5/04 01:39:20 PM
BIOPHARMACEUTICS

Sally Yasuda
11/5/04 02:31:22 PM
BIOPHARMACEUTICS

REQUEST FOR CONSULTATION

Andre

TO (Division/Office):
860/Biopharm

FROM:
HFD-120/ Division of Neuropharmacological Drug Products

DATE
10/18/04

IND NO.

NDA NO.
21-476

TYPE OF DOCUMENT

DATE OF DOCUMENT
June 14, 2004

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Estorra (Eszopiclone)

NAME OF FIRM: Sepracor

REASON FOR REQUEST

DELIVERED OCT 19 2004

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

I am covering for Merrill Mille on this NDA. A biopharm consult was needed on the June 14, 2004 submission, but to my understanding a consult was not sent. Please review the submission and provide any appropriate feedback for the sponsor. Andre Jackson is the assigned reviewer for this NDA and to my understanding already has a copy of the submission. If you have any questions please contact me at 301-594-5535 or email at gujralr@cderr.fda.gov. Thank you.

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Eric

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

DRUG: Estorra ® (Eszopiclone)

PRIMARY REVIEWER: Andre Jackson

NDA: 21476

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 2 mg, 3 mg

APPLICANT: Sepracor Inc.

Submission Date: January 30, 2003

March 25, 2003

June 13, 2003

July 13, 2003

INDICATIONS: Insomnia

Generic Name: Eszopiclone

1.0 Executive Summary

Racemic (RS)-zopiclone was originally developed by Rhône-Poulenc Rorer (RPR) and is currently marketed by RPR in 85 countries, including Great Britain, France, Germany, Canada, Norway, Sweden, and Japan under the trade names Amoban[®], Datolan[®], Datovane[®], Foltran[®], Imovane[®], Limovane[®], Siaten[®], Ximovan[®], and Zimovane[®].

Zopiclone is a cyclopyrrolone derivative and as such, belongs to a chemical class that is structurally unrelated to other existing hypnotic drugs. Zopiclone is believed to act as a positive allosteric agonist at GABA_A receptors. The GABA_A-macromolecular complex mediates the majority of inhibitory neurotransmission in mammalian brain and comprises a class of ligand-gated ion channels that control chloride ion flux across neuronal cell membranes. Drugs interacting with these receptors exert a wide spectrum of pharmacological effects, including regulation of anxiogenic and epileptogenic activities, as well as states of vigilance, sedation, and muscle tension.

Zopiclone is the S-isomer of racemic zopiclone. The NDA was submitted for the treatment of insomnia utilizing the 2 mg and 3 mg tablet strengths of zopiclone tablets.

The *in vitro* pharmacodynamics of racemic zopiclone were characterized as stereoselective, with the affinity for the (S)-enantiomer determined to be ~50 times greater than the (R)-enantiomer.

Six randomized double-blind placebo control parallel group clinical studies were submitted to support the insomnia indication. The key efficacy measures for Eszopiclone (the product is also referred to by the firm as zopiclone, esopiclone and (S)-zopiclone) were objective latency to persistent sleep (LPS), objective sleep efficiency, objective wake time after sleep onset (WASO), subjective sleep latency, and subjective total sleep time.

Twenty Phase I studies have been conducted by Sepracor, Inc. to describe the human pharmacology and bioavailability/bioequivalence of esopiclone and its inactive metabolites, (S)-desmethylzopiclone and N-oxide-zopiclone, following oral administration. Further, there were 8 drug-drug interaction studies.

The focus of this NDA is the active moiety, i.e. the parent drug.

Esopiclone was rapidly absorbed following oral administration, with t_{max} occurring at 1 hour post-dose in healthy subjects. Esopiclone is 52-59% bound to plasma proteins in healthy subjects with red cell partitioning of 0.31-0.34 over the concentration range of 5-500 ng/mL. Esopiclone is metabolized by CYP3A4 and CYP2E1 to (S)-desmethylzopiclone and N-oxide-zopiclone. Renal excretion is the principal route of elimination of esopiclone and its metabolites. Up to 75% of an oral dose of racemic ^{14}C -zopiclone was excreted in the urine primarily as metabolites. A similar excretion profile would be expected for esopiclone, because of the observed equivalency in the metabolic clearance of esopiclone in the presence or absence of (R)-zopiclone and the formation of the same metabolites. Less than 10% of the dose was excreted in the urine as unchanged drug. The pharmacokinetics for esopiclone are linear. The plasma concentration profile of esopiclone was characterized by a bi-exponential decline with an apparent terminal phase $t_{1/2}$ of approximately 6 hours. Esopiclone exhibited dose-proportional pharmacokinetics over the range of 1.0 to 6.0 mg QD. No accumulation of esopiclone was observed following 7 days of once daily drug administration in normals. However an accumulation ratio of approximately 1.6 was observed for AUC in elderly. At steady-state females had a 25% higher exposure than males based upon $AUC(0-\tau)$. There were no other noteworthy gender or racial differences in other pharmacokinetic parameters.

Plasma concentrations of (S)-zopiclone were greater than (R)-zopiclone and the $t_{1/2}$ of (S)-zopiclone was about twice that of (R)-zopiclone. A similar pattern was observed for the (S)-desmethylzopiclone metabolite. There was no interconversion between (S)-zopiclone and (R)-zopiclone.

Systemic exposure increased by 41% in the elderly (≥ 65 years of age) compared to non-elderly adults. It appears that a decrease of esopiclone dose from 3.0 to 2.0 mg is warranted in the elderly. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. Systemic exposure increased by 2 fold in subjects with severe hepatic impairment. Systemic exposure increased by 47% in subjects with severe renal impairment. No dosage adjustment appears necessary in subjects with renal impairment since less than 10% of esopiclone is excreted unchanged in the urine, however, these subjects should be closely monitored.

There was a 2 fold increase in AUC and a 1.5 fold increase in C_{max} for esopiclone in the presence of steady-state ketoconazole levels. There was also a 15% decrease in AUC and a 20% decrease in C_{max} for ketoconazole in the presence of steady-state esopiclone levels. A reduction in esopiclone dose to 2.0 mg is proposed upon co-administration with potent CYP3A4 inhibitors.

The pharmacokinetics and anticoagulant properties of (RS)-warfarin were not affected by co-administration of esopiclone. A dose adjustment of (RS)-warfarin is not required when co-administered with esopiclone. Esopiclone had no effect on the pharmacokinetics of digoxin. A dose adjustment for digoxin is not required upon co-administration with esopiclone. There was a 20% decrease in C_{max} for esopiclone in the presence of

lorazepam. The administration of esopiclone with lorazepam as the substrate resulted in a 20% decrease in Cmax for lorazepam.

There was no effect of paroxetine on esopiclone pharmacokinetics and also no effect of esopiclone on paroxetine as the substrate.

(S)-zopiclone did not inhibit the in vitro activities (IC50) of CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in human hepatocytes.

Cmax levels are lowered 22% by food while Tmax was delayed by 1 hour. The to-be marketed 2 mg and 3 mg tablets were determined to be bioequivalent to the clinical batches. Zopiclone dissolution was investigated in 3 media and a dissolution method and specification are being set in this NDA.

1.1 RECOMMENDATIONS

1. The Clinical Pharmacology and Biopharmaceutics section of NDA 21-476 is acceptable to OCPB.

1.2 COMMENTS TO THE CLINICAL DIVISION/MEDICAL OFFICER

1. Please verify the following statement in labeling:

Olanzapine

Co administration of esopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores.

2. The firm is encouraged to develop a lower strength and or a scored 2 mg tablet. In liver patients only the 2 mg dose was studied which resulted in a 2 fold increase in exposure. If a lower dose were available OCPB would have recommended that this dose be used in severely hepatically impaired patients.

1.3 COMMENTS TO THE SPONSOR

1. The sponsor is requested to adopt the following dissolution method and specification for the 2mg and 3 mg strengths of esopiclone tablets

Summary of Drug Product Dissolution Method and Specification

Dosage Form	Esopiclone Tablets
Strengths	2.0 and 3.0 mg
Apparatus	USP Type 2 apparatus (paddle)
Media	
Volume	/
Speed of Rotation	
Acceptance Criterion	Q: - at 30 minutes

2. Please incorporate OCPB labeling text and changes from pages 32-34, 43 and 51 into your final labeling for esopiclone.

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2.0 INTRODUCTION

(S)-Zopiclone is the active enantiomer of (RS)-zopiclone, a short-acting hypnotic agent. Racemic (RS)-zopiclone was originally developed by Rhône-Poulenc Rorer (RPR) and is currently marketed by RPR in 85 countries, including Great Britain, France, Germany, Canada, Norway, Sweden, and Japan under the trade names Amoban[®], Datolan[®], Datovane[®], Foltran[®], Imovane[®], Limovane[®], Siaten[®], Ximovan[®], and Zimovane[®].

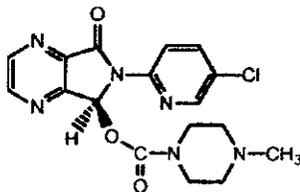
Zopiclone is a cyclopyrrolone derivative and as such, belongs to a chemical class that is structurally unrelated to other existing hypnotic drugs. Zopiclone is believed to act as a positive allosteric agonist at GABA_A receptors. The GABA_A-macromolecular complex mediates the majority of inhibitory neurotransmission in mammalian brain and comprises a class of ligand-gated ion channels that control chloride ion flux across neuronal cell membranes. Drugs interacting with these receptors exert a wide spectrum of pharmacological effects, including regulation of anxiogenic and epileptogenic activities, as well as states of vigilance, sedation, and muscle tension. A variety of distinct modulatory binding sites have been identified on GABA_A receptors, including those for anesthetics, barbiturates, alcohol, benzodiazepines and non-benzodiazepine hypnotics, and neurosteroids. Although zopiclone can displace benzodiazepines from central binding sites, it is not certain that cyclopyrrolones and benzodiazepines bind to the same site within the GABA_A receptor complex, or whether they interact allosterically via closely located binding domains. In fact, several studies showed that zopiclone was not bound to the benzodiazepine binding site, but rather to a related site on the GABA_A complex. In *in vitro* studies, zopiclone showed high affinity for binding sites in the cerebral cortex, hippocampus, and cerebellum. No information is presently available as to the stereoselectivity of any of these characteristics of zopiclone. So far, only the *in vitro* pharmacodynamics of zopiclone has been characterized as being stereoselective. The affinity has been determined to be approximately 50 times greater for (S)-zopiclone than (R)-zopiclone. Another study indicated that (S)-zopiclone had approximately twice the potency of the racemate at benzodiazepine binding sites. Thus, due to the greater affinity of (S)-zopiclone for the binding site associated with hypnotic/anxiolytic activity, it is presumed that (S)-zopiclone accounts for most of the pharmacological activity of (RS)-zopiclone.

3.0 QUESTION BASED REVIEW

3.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

ESTORRA (eszopiclone) is a nonbenzodiazepine anti-insomnia agent, which is a pyrrolopyrazine derivative of the cyclopyrrolone class. The chemical name of eszopiclone is (+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate. Its molecular weight is 388.81 and its empirical formula is C₁₇H₁₇ClN₆O₃. Eszopiclone has a single chiral center with an (S)-configuration. It has the following chemical structure:



Eszopiclone is a white to light yellow crystalline solid. Eszopiclone is slightly soluble in ethanol, and very slightly soluble in water.

Eszopiclone is formulated as film-coated tablets for oral administration. ESTORRA tablets contain either 2 mg or 3 mg eszopiclone.

It has a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties. Cyclopyrrolones interact with GABA-receptor macromolecular complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. They act to potentiate increased GABA-evoked chloride conductance resulting in neuronal hyperpolarization and thereby inhibiting neuronal transmission and causing sleep.

Racemic zopiclone has been marketed (primarily outside the US) since 1987, primarily at a dose of 7.5 mg (3.75 mg for the elderly and in patients with impaired liver function or chronic respiratory insufficiency).

What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data ?

The key efficacy measures include objective latency to persistent sleep (LPS), objective sleep efficiency, objective wake time after sleep onset (WASO), subjective sleep latency, and subjective total sleep time. The primary efficacy endpoint was objective latency to

persistent sleep (LPS), defined as the time from lights out to the first of 20 consecutive 30-second epochs (10 minutes) of sleep. Hypnotic efficacy was measured objectively [polysomnographic (PSG) recording] and subjectively (morning questionnaires). Centralized scoring was used for evaluation of the PSG recordings. Objective sleep efficiency, defined as the total sleep time expressed as a percent of the total recording time, was the key secondary endpoint. Other secondary efficacy endpoints included objective number of awakenings (number of times awake during sleep) and other objective and subjective sleep parameters.

Several studies specifically evaluated withdrawal and next day performance effects. These were accomplished through additional assessments, such as Cognitive Drug Research (CDR) measures, Digit Symbol Substitution Test (DSST), and subjective measures.

3.2 GENERAL CLINICAL PHARMACOLOGY

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

3.2.1 EFFICACY ENDPOINTS

These measures were selected to support the indication for reduced sleep latency and improved sleep maintenance. Primary Endpoint for studies with objective measures (190-026, 190-045, and 190-046), objective latency to persistent sleep (LPS) was the primary efficacy measure. LPS and objective sleep efficiency were co-primary measures in Study 190-047. For Studies 190-048 and 190-049, subjective sleep latency was the primary efficacy measure. For Studies 190-026, 190-046, and 190-045, objective sleep efficiency was a key secondary efficacy measure. Objective wake time after sleep (WASO) onset was designated as a key secondary measure for studies 190-045, 190-046, and 190-047. For the entirely subjective studies, 190-048 and 190-049, subjective total sleep time was designated as the key secondary efficacy measure. Hypnotic efficacy was measured objectively [polysomnographic (PSG) recording] and subjectively (morning questionnaires). Other secondary endpoints included objective wake time before persistent sleep; objective and subjective wake time after sleep onset; objective and subjective number of awakenings; objective wake time during sleep; objective wake time after sleep; objective total time and percent of sleep time in NREM Stage 1, 2, and 3+4; objective total time and percent of sleep time in REM sleep; subjective quality of sleep; and subjective depth of sleep.

3.2.2 EXPOSURE RESPONSE RELATIONSHIPS

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The metabolites for (S) zopiclone i.e., (S) desmethylzopiclone and N-oxide-zopiclone are inactive although the firm did develop an analytical method suitable for parent drug and metabolites. The active moiety is the parent drug.

3.2.3 DOSE PROPORTIONALITY

What is the degree of linearity or nonlinearity in the dose-concentration relationship?

Table 1 : Dose Proportionality of (S)-Zopiclone AUCinf following Oral Administration of (S)-Zopiclone at single doses between 1.0 and 7.5 mg and (RS)-Zopiclone at doses between 2.5 and 7.5 mg.

	(S)-Zopiclone	(RS)-Zopiclone
Slope Estimate	1.071	1.119
Slope Std Error	0.065	0.103
95% CI	0.941-1.202	0.901-1.337

The slopes indicate linear kinetics following single doses.

Cmax values following single dosing were also dose proportional.

Table 2. Slope Estimates and 95% Confidence Intervals from the Assessment of Dose proportionality following multiple dosing (1-6 mg) in healthy normals using the power model.

Analyte	Parameter	Estimate ¹	Slope Estimates and Confidence Intervals				
			Day 1		Day 7		
			95% CI		95% CI		
			Lower	Upper	Estimate ¹	Lower	Upper
(S)-Zopiclone	Cmax	0.91	0.78	1.05	1.00	0.87	1.12
	AUC(0-24)	0.98	0.84	1.13	1.00	0.85	1.15

¹ Slope estimate (b) from power model, $\log(\text{parameter}) = a + b * \log(\text{dose}) + \text{error}$.

Slopes indicate linear kinetics for AUC (0-24hrs) and Cmax following multiple dosing.

Linear kinetics for AUC (0-t) and Cmax were also exhibited for the elderly following single dosing of (S)-zopiclone in study 190-005.

3.2.4 GENERAL PHARMACOKINETICS AND CHRONIC DOSING

Do PK parameters change with time following chronic dosing?

Table 3. Accumulation Ratios for (S)-Zopiclone in healthy normals

Analyte	Parameter	Statistic	Multiple Dose		
			Period 2, Day 7 (Fasted)		
(S)-Zopiclone	RAUC (ng*hr/mL)	n	6	11	12
		Mean	1.06	1.07	1.09
	SD	0.18	0.18	0.13	
	RCmax (ng*hr/mL)	n	11	12	12
		Mean	0.97	1.04	1.15
	SD	0.24	0.17	0.37	

RAUC: Accumulation ratio for AUC(0-24) calculated as [AUC(0-24) Period 2, Day 7] / [AUC(0-24) Period 2, Day 1].

RCmax: Accumulation ratio for RCmax calculated as [RCmax Period 2, Day 7] / [RCmax Period 2, Day 1].

Table 4. Accumulation Ratios for (S)-Zopiclone for elderly based upon mean data (Day7/Day1)

Analyte	Parameter	Statistic	Multiple Dose			
			Period 2, Day 7 (Fasted)			
(S)-Zopiclone	RAUC(0-inf) (ng*hr/mL)	Mean	1.38	1.58	1.56	1.36
		RCmax (ng*hr/mL)	Mean	1.13	1.21	1.27

Theoretical accumulation ratios based upon $1/1 - e^{-k \cdot \tau}$ were 1.01 for normals (average half-life 4 hrs) and 1.06-1.18 for elderly with average half-lives from 6-9 hrs.

3.2.4.1 Gender and Race

Results from a meta analysis of the data indicated that at steady-state there was a 25% increase in dose normalized (i.e., to 1 mg) AUC (0-tau) in females compared to males for all races. There was one caucasian female age 76 that was dosed with 3 mg of (S)-zopiclone with a normalized AUC (0-tau) value of 224 ngxhr/ml which tended to increase the mean for all females and caucasians. There was a 12% decrease in dose normalized AUC (0-tau) in black males and females compared to caucasians. All changes in Cmax for race and gender were less than 12%.

3.2.5 S AND R INTERCONVERSION

Was there any evidence of in vivo interconversion between S and R Zopiclone?

Studies were done (N=6, at each dose) using an oral solution with doses of 2.5 mg, 5.0 mg and 7.5 mg of RS-zopiclone and doses of 1.0mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.75 mg, 5.0 mg and 7.5 mg of S-zopiclone. R and S zopiclone were measured for the racemic mixture. The racemic mixture doses of 7.5 mg and 5.0 mg were compared with the S-zopiclone 3.75 mg and 2.5 mg doses respectively.

Table 5. Summary of mean (S)- zopiclone ratios following oral administration for the 7.5 mg and 5.0 mg dose racemic tablets compared to the 3.75 mg and 2.5 mg S zopiclone tablets respectively.

Parameter	7.5mg solution RS Zopiclone /3.75 mg solution S Zopiclone	5.0mg solution RS Zopiclone /2.5 mg solution S Zopiclone
Cmax	36.47/24.78=1.47	20.83/27.07=0.76
AUCt	255.8/217.3=1.17	149.2/155.9=0.95
AUCinf	267.5/232.5=1.15	160.0/174.4=0.91

Table 6. Summary of mean S/R zopiclone ratios for Cmax following oral administration of the 2.5 mg, 5.0 mg and 7.5 mg dose racemic solutions.

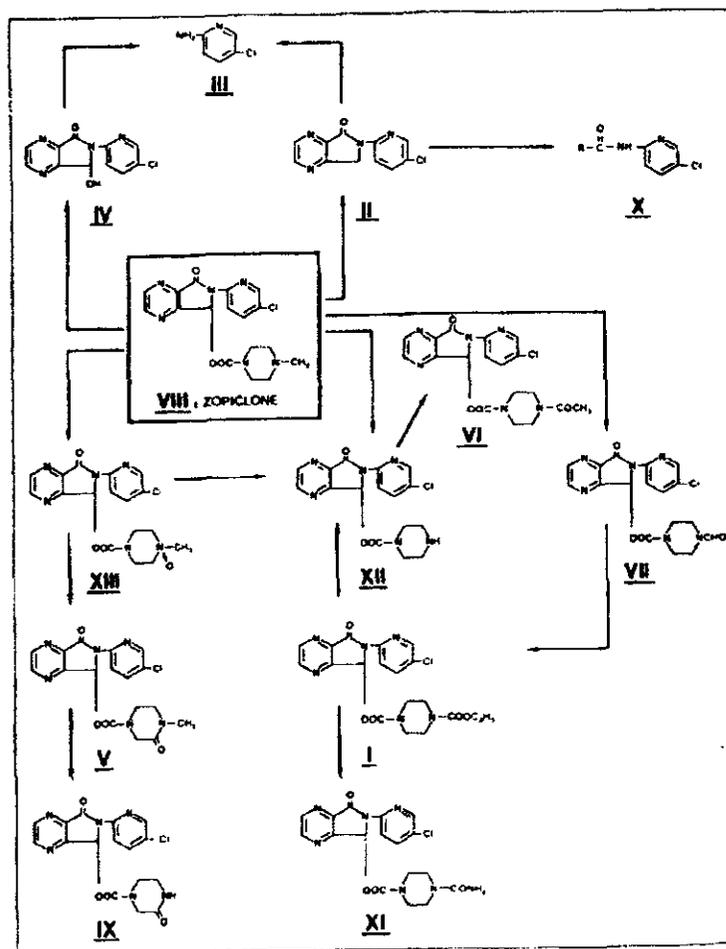
Dose RS	S-zopiclone ng/ml-Cmax	R-zopiclone ng/ml-Cmax	RatioS/R
2.5 mg	11.42	8.13	1.4
5.0 mg	20.83	12.36	1.68
7.5 mg	36.47	25.42	1.43

Table 7. Summary of mean S/R zopiclone AUC(0-t) ratios following oral administration of the 2.5 mg, 5.0 mg and 7.5 mg dose racemic solutions.

Dose RS	S-zopiclone ng/mlxhr AUCt	R-zopiclone ng/mlxhr AUCt	RatioS/R
2.5 mg	67.1	25.7	2.6
5.0 mg	149.2	55.8	2.6
7.5 mg	255.8	104.5	2.4

There was no evidence of R-S interconversion since constant dose independent S/R ratios were observed for the different dosage formulations.

3.2.6 MAJOR ROUTES OF ELIMINATION



What is the proposed metabolic scheme for (S)-zopiclone?

CYP3A4 appears to be responsible for about 40% of both N-oxidation (XIII) and N-desmethylation (XII) of zopiclone while the CYP2E1 subfamily accounts for about 40% of N-desmethylation.

Do Mass Balance studies suggest renal or hepatic route as the major route of elimination?

A study was done in 6 male volunteers. Each subject received a single 7.5 mg oral dose of ^{14}C -Zopiclone as a gelatin capsule.

The per cent recovery of radioactivity as per cent of dose was:

Feces-15.8%
Urine-75%

Less than 6% of the drug is excreted in the urine as (S)-zopiclone.

What are the important in vitro intrinsic factors related to the exposure of eszopiclone?

3.3 IN VITRO PERFORMANCE

3.3.1 PROTEIN BINDING AND RED CELL PARTIONING

What was the protein binding and red cell partitioning for esopiclone?

In vitro blood-to-plasma partitioning ratios in humans were 0.31-0.34 over the concentration range of 5-500 ng/mL. In vitro plasma protein binding of (S)-zopiclone in humans was 53-59% over the concentration range of 5-500 ng/mL.

3.3.2 IN VITRO DRUG INTERACTIONS

Did any in vitro hepatocyte studies indicate which CYP enzyme systems would be involved in esopiclone metabolism?

In vitro hepatocyte studies using a 15 min pre-incubation with 5 uM of ketoconazole indicated that the rate of parent drug disappearance decreased to 72%, 45% and 64% for esopiclone concentrations of 10 uM (3880 ng/ml)-(level is 100x Cmax observed for clinical doses) , 100uM and 200 uM respectively. This result indicated that CYP3A4 may be involved in esopiclone metabolism.

Another study pre-incubating microsomes with 100 uM of 4-methylpyrazole indicated that the rate of parent drug disappearance decreased to 62%, 71% and 74% for esopiclone concentrations of 10 uM, 100uM and 200 uM respectively indicating that CYP 2E1 may be involved in esopiclone metabolism.

Is the drug an inhibitor and/or an inducer of CYP enzymes?

Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.

3.4 EXTRINSIC FACTORS

What type of drug-drug interactions were investigated for Esopiclone?

The following drug-drug interaction studies were done for esopiclone:

Drug	Study #
Ketoconazole(antifungal)	190-023
Warfarin(anticoagulant)	190-021
Digoxin(cardiac glycoside)	190-022
Olanzapine(schizophrenia)	190-018
Lorazepam(antianxiety)	190-019
Paroxetine(depression)	190-020
Ethanol	190-015-Clinical Study-No PK

Were there any study design issues related to the drug-drug interaction studies?

The drug-drug interaction studies were designed in accordance with the actual clinical use of the interacting drug.

<u>Drug</u>	<u>Recommended Regimen</u>	<u>NDA Dosing</u>
Ketoconazole	Single Daily Doses 200 mg	Single Daily Doses 400 mg
Warfarin	Individualized	Single Daily Dose 25 mg
Digoxin	Titrated	Day 1 Daily Dose of 0.5 mg as bid then Day 2-7 Single Daily Doses of 0.25 mg
Olanzapine	Single Daily Dose 5-10 mg	Single Daily Dose 10 mg
Lorazepam	2-6 mg/day divided doses	Single Daily Dose 2 mg
Paroxetine	Single Daily Dose 20-30 mg	Single Daily Dose 20 mg

The design of the drug-drug interaction studies were consistent with the dosage recommendations except for ketoconazole where the higher dose of ketoconazole was used to allow complete inhibition of CYP3A4.

In the case of Warfarin the prothrombin time and international normalization ratio were measured to show that there were no pharmacodynamic interactions. A point that should be noted in all of these studies was that although esopicone will be administered clinically in the evening all drug-drug interaction studies were done in the morning. Therefore any of the observed drug-drug interactions may be impacted due to diurnal effects which were not investigated.

Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

3.4.1 Ketoconazole-Study 190-023

Ketoconazole, a broad-spectrum antifungal agent, is known to be a potent inhibitor of the CYP3A4 enzyme system and affects the metabolism of a variety of drugs including cyclosporine and phenytoin. The study was done as a single-center, inpatient, three-way crossover, open-label, multiple dose study. Subjects were randomized to receive a sequence of the following treatments: 400 mg of ketoconazole (2 x 200 mg tablets) daily

for five days (Treatment A), 3 mg esopiclone (2 x 1.5 mg tablets) daily for five days (Treatment B), or 3 mg of esopiclone (2 x 1.5 mg tablets) co-administered with 400 mg of ketoconazole (2 x 200 mg tablets) daily for five days (Treatment C).

Was there a significant effect of Ketoconazole on esopiclone as the substrate or of esopiclone on ketoconazole when esopiclone is the interacting drug?

Table 8: Treatment Comparison of Esopiclone Pharmacokinetic Parameters in the presence of Ketoconazole.

Parameter	Treatment	N	Geometric	Combination versus Monotherapy	
			LS Mean	Ratio (%)	90% CI
AUC _(0-τ) (hr*ng/ml)	Esopiclone	17	250.8	-	-
	Esopiclone + Ketoconazole	18	563.3	224.63	(208.5, 242.0)
C _{max} (ng/ml)	Esopiclone	17	38.6	-	-
	Esopiclone + Ketoconazole	18	55.2	143.09	(130.0, 157.5)
t _{1/2} (hr)	Esopiclone	17	7.0	-	-
	Esopiclone + Ketoconazole	18	9.2	131.83	(124.7, 139.4)
t _{max} ^a (hr)	Esopiclone	17	1.0	-	-
	Esopiclone + Ketoconazole	18	1.0	-	-

^a t_{max} is rank-transformed and median is presented instead of geometric LSmean.

Table 9: Treatment Comparison of Ketoconazole Pharmacokinetic Parameters in the presence of Esopiclone.

Parameter	Treatment	N	Geometric	Combination versus Monotherapy Comparison	
			LS Mean	Ratio (%)	90% CI
AUC(0- τ) (hr* μ g/ml)	Ketoconazole	18	68.3	-	-
	Esopiclone + Ketoconazole	18	59.7	87.51	(73.7, 103.9)
C _{max}	Ketoconazole	18	9.1	-	-

(µg/ml)	Esopiclone + Ketoconazole	18	7.4	81.95	(70.9, 94.7)
t1/2 (hr)	Ketoconazole	18	5.2	-	-
	Esopiclone + Ketoconazole	18	5.4	102.92	(90.1, 117.5)
tmax ^a (hr)	Ketoconazole	18	2.0	-	-
	Esopiclone + Ketoconazole	18	2.0	-	-
^a tmax is rank-transformed and median is presented instead of geometric LSmean.					

1. There was a 2 fold increase in AUC and a 1.5 fold increase in Cmax for esopiclone in the presence of steady-state ketoconazole levels.
2. There was a 10% decrease in AUC and a 20% decrease in Cmax for ketoconazole in the presence of steady-state esopiclone levels.
3. The results indicate that the esopiclone dose could be reduced when any drug which is an inhibitor of CYP3A4 is administered concomitantly.

3.4.2 Lorazepam- Study 190-014

Was there a significant drug effect of esopiclone on Lorazepam or Lorazepam on esopiclone?

The study was done as a single-center, inpatient, randomized, daytime dosing, single-blind, four-arm, parallel, single dose study using oral doses of 3 mg (S)-zopiclone and 2 mg lorazepam in 36 healthy volunteers ages 21-64 years.

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Table 10. Esopiclone parameters in the presence of lorazepam.

Parameter	Treatment	N	Mean ± SD ¹	Combination versus Monotherapy comparison			
				Geometric LS mean ²	Ratio (%) ³	90% CI for Ratio	p-value
C _{max} (ng/ml)	(S)-Zopiclone	9	38.09 ± 9.75	36.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	29.28 ± 7.09	28.5	77.40	[62.3, 96.1]	0.0552
AUC _(0-12h) (ng*hr/ml)	(S)-Zopiclone	9	248.72 ± 47.61	244.5	-	-	-
	(S)-Zopiclone + Lorazepam	9	236.46 ± 69.53	227.3	92.99	[75.4, 114.7]	0.5542
t _{1/2} (hr)	(S)-Zopiclone	9	5.70 ± 0.98	5.6	-	-	-
	(S)-Zopiclone + Lorazepam	9	5.73 ± 0.91	5.7	100.61	[87.6, 115.5]	0.9397
t _{max} (hr)	(S)-Zopiclone	9	1.00 ¹	-	-	-	-
	(S)-Zopiclone + Lorazepam	9	1.00	-	-	-	0.7115

¹t_{max} provided as Median [Range]

²Geometric LS mean: Geometric least-squares mean. All parameters except t_{max} were log_e transformed. Values of t_{max} were rank-transformed prior to the analysis.

³Ratio (%) of the geometric least-squares means (LS means) for the log_e transformed analysis.

Table 11. Lorazepam parameters in the presence of esopiclone.

Parameter	Treatment	N	Mean ± SD ¹	Combination versus Monotherapy comparison			
				Geometric LS mean ²	Ratio (%) ³	90% CI for Ratio	p-value
C _{max} (ng/mL)	Lorazepam	9	27.80 ± 11.56	26.1	-	-	-
	(S)-Zopiclone + Lorazepam	9	21.57 ± 7.54	20.6	78.68	[59.5, 104.0]	0.1532
AUC _(0-12h) (ng*hr/mL)	Lorazepam	9	320.85 ± 105.12	304.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	287.51 ± 86.67	275.9	90.48	[69.1, 118.4]	0.5260
t _{1/2} (hr)	Lorazepam	9	15.69 ± 5.33	14.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	19.91 ± 7.87	18.8	125.61	[95.1, 165.9]	0.1720
t _{max} (hr)	Lorazepam	9	1.50	-	-	-	-
	(S)-Zopiclone + Lorazepam	9	1.55	-	-	-	0.5302

¹t_{max} provided as Median [Range]

²Geometric LS mean: Geometric least-squares mean. All parameters except t_{max} were log_e transformed. Values of t_{max} were rank-transformed prior to the analysis.

³Ratio (%) of the geometric least-squares means (LS means) for the log_e transformed analysis.

1. The co-administration of (S)-zopiclone (substrate) with lorazepam decreased the (S)-zopiclone mean C_{max} by 23% (90% CI: 62.3, 96.1). There was a 5% decrease in AUC.
2. There was no difference in the median t_{max} of (S)-zopiclone when administered as (S)-zopiclone monotherapy or concomitantly with lorazepam (median t_{max} = 1 hour). The mean $t_{1/2}$ for (S)-zopiclone was not affected by co-administration of lorazepam (mean $t_{1/2}$ = 5.70 hours and 5.73 hours, respectively).
3. The co-administration of lorazepam (substrate) with (S)-zopiclone decreased the lorazepam mean C_{max} by 22% (90% CI: 59.5, 104.0) and the lorazepam mean AUC (0-last) by 10% (90% CI: 69.1, 118.4).
4. Based upon the observed changes in esopiclone levels in the presence of lorazepam and when lorazepam was the substrate, there does not appear to be a need to change the dose for either drug in the presence of the other.

3.4.2 OLANZAPINE- Study 190-018

Was there a significant drug effect of esopiclone on Olanzapine or for Olanzapine on esopiclone?

The study was done as a single center, inpatient, randomized, four-arm parallel, daytime administration, single-dose, single-blind study in 40 healthy adult volunteers.

Administered doses were : Placebo esopiclone; esopiclone 3.0 mg (2 x 1.5 mg); Olanzapine 10 mg (1 x 10 mg); Olanzapine (1 x 10 mg) plus esopiclone 3.0 mg (2 x 1.5 mg).

Table 12: Treatment Comparison of Esopiclone Pharmacokinetic Parameters

Parameter	Treatment	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-last)	Monotherapy	10	227.0	106.02	(89.9, 125.1)	-
	Combination	10	240.7			
C_{max}	Monotherapy	10	38.5	97.08	(81.3, 115.9)	-
	Combination	10	37.4			
$t_{1/2}$	Monotherapy	10	5.9	106.72	(90.6, 125.6)	-
	Combination	10	6.3			
t_{max} ^c	Monotherapy	10	0.8	-	-	0.4683
	Combination	10	1.0			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was analyzed by the Wilcoxon Rank-Sum test and the median is reported under the Geometric LS Mean.

Table 13. Treatment Comparison of Olanzapine Pharmacokinetic Parameters

Parameter	Comparison	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-12h)	Combination	10	509.3	95.56	(81.1, 112.6)	-
	Monotherapy	10	532.9			
C _{max}	Combination	9	16.6	91.64	(74.7, 112.5)	-
	Monotherapy	9	18.1			
t _{1/2}	Combination	10	38.7	108.34	(87.1, 134.8)	-
	Monotherapy	10	35.8			
t _{max} ^c	Combination	9	6.0	-	-	0.0777
	Monotherapy	9	4.0			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was analyzed by the Wilcoxon Rank-Sum test and the median is reported under the Geometric LS Mean.

Olanzapine following a single dose of 10 mg did not have an effect on esopiclone plasma parameters. Also a 3 mg single dose of Esopiclone had no effect on Olanzapine plasma concentrations. No dose adjustment is required for either esopiclone or Olanzapine.

3.4.3 PAROXETINE Study 190-020

Was there a significant drug effect of esopiclone on paroxetine or paroxetine on esopiclone?

This was a single-center, inpatient, randomized, four-arm parallel, daytime administration, single-dose, single-blind study in normal healthy male and female volunteers. Forty subjects were enrolled. Subjects received placebo, 3 mg esopiclone alone and 20 mg paroxetine alone and 3 mg esopiclone with 20 mg paroxetine. An original 24 subjects were dosed and additional 16 were dosed several months after the original cohort.

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Table 14. Esopiclone Pharmacokinetic Parameters in the presence of paroxetine.

Parameter	Treatment	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-12h)	Monotherapy	10	215.1	109.25	(90.3, 132.2)	0.4306
	Combination	10	235.0			
C _{max}	Monotherapy	10	27.7	111.63	(94.8, 131.4)	0.2582
	Combination	10	30.9			
t _{1/2}	Monotherapy	10	6.0	116.53	(95.7, 141.8)	0.1939
	Combination	10	7.0			
t _{max} ^c	Monotherapy	10	1.3 ^d	-	-	1.0000 ^e
	Combination	10	1.3 ^d			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was rank-transformed

^d Median

^e p-value for the testing the difference in the medians.

Table 15. Paroxetine Pharmacokinetic Parameters in the presence of esopiclone.

Parameter	Comparison	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-12h)	Monotherapy	10	71.5	96.45	(34.0, 273.9)	0.9527
	Combination	9	69.0			
C _{max}	Monotherapy	10	7.0	101.62	(52.5, 196.5)	0.9666
	Combination	9	7.1			
t _{1/2}	Monotherapy	8	10.5	99.43	(56.5, 175.0)	0.9858
	Combination	4	10.5			
t _{max} ^c	Monotherapy	10	4.0 ^d	-	-	0.3219 ^e
	Combination	9	4.0 ^d			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was rank-transformed

^d Median

^e p-value for the testing the difference in the medians.

Paroxetine following a single dose of 20 mg did not have an effect on esopiclone (substrate) plasma parameters. Also a 3 mg single dose of esopiclone had no effect on paroxetine (substrate) plasma concentrations therefore, no dose adjustment is required for either drug.

3.4.4 DIGOXIN- PROTOCOL NO.: 190-022

Was there a significant drug effect of esopiclone on digoxin?

This was a single-center, in-patient, open label, multi-daytime-dose study in healthy male and female subjects between the ages of 21 and 64, inclusive. Twelve subjects were enrolled and received two 0.5 mg doses of digoxin on Day 1, taken 12 hours apart, followed by single daily doses of 0.25 mg digoxin from Day 2 through Day 7. On Day 7, subjects received digoxin in combination with a single 3 mg oral dose of (S)-zopiclone.

Table 16: Treatment Comparison of Digoxin Pharmacokinetic Parameters

Parameters	Comparison	Geometric LSmean ¹		Ratio	90% CI	p-value
		(S)-Zopiclone + Digoxin	Digoxin Alone			
C _{max}	Combination/Alone	2.0	2.3	87.7	(80.1, 96.1)	----
AUC _(0-τ)	Combination/Alone	20.8	21.0	99.2	(96.9, 101.6)	----
t _{max} ²	Combination/Alone	1.0	1.0	----	----	0.0684

¹ Geometric LSmean: anti-log of least-squares means derived from the linear model on log-transformed data.
² For t_{max}, the median and the p-value for treatment effect from the ANOVA model were presented.

The 90% confidence intervals of the ratios for C_{max} (Ratio: 87.7; 90% CI: 80.1, 96.1) and AUC_(0-τ) (Ratio: 99.2; 90% CI: 96.9, 101.6) were within the 80-125% range demonstrating that the pharmacokinetic profile of digoxin was not affected when digoxin was taken with (S)-zopiclone. The effect of digoxin on esopiclone was not studied.

3.4.5(R, S)-WARFARIN- PROTOCOL NO.: 190-021

Was there a significant drug effect of esopiclone on warfarin ?

This was a single-center, in- and out-patient, randomized, multiple daytime dosing, complete cross-over, two-treatment, open-label study in healthy adults. Subjects were randomized to receive one of the following treatment sequences AB or BA in a crossover fashion with a 14-day washout between treatments.

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Treatment Sequence	Visit 2	Visit 3
I	(R,S)-Warfarin Single 25 mg dose (Treatment A)	5x daily doses of 3 mg esopiclone, with (R,S)-warfarin 25 mg dose in combination with the last esopiclone dose (Treatment B)
II	5x daily doses of 3 mg esopiclone, with (R,S)-warfarin 25 mg dose in combination with the last esopiclone dose (Treatment B)	(R,S)-Warfarin Single 25 mg dose (Treatment A)

Pharmacokinetic data are presented in the Appendix.

The pharmacokinetics of (R)-warfarin following a single dose (R, S)-warfarin given alone were not statistically significantly different to those following a single dose of (R,S)-warfarin given in combination with esopiclone at steady state. The 90% confidence intervals of ratios of geometric least squared means of a single dose of (R,S)-warfarin given with esopiclone to a single dose of (R,S)-warfarin alone for $AUC_{(0-last)}$ (93.7%, 102.8%) and C_{max} (82.5%, 100.6%) fell between 80 and 125%.

The pharmacokinetics of (S)-warfarin following a single dose (R,S)-warfarin given alone were not statistically significantly different to those following a single dose of (R,S)-warfarin given in combination with esopiclone at steady state. The 90% confidence intervals of ratios of geometric least squared means of a single dose of (R,S)-warfarin given with esopiclone to a single dose of (R,S)-warfarin alone for $AUC_{(0-last)}$ (92.6%, 104.9%) and C_{max} (81.9%, 101.5%) fell between 80 and 125%.

For AUC_{INR} and INR_{max} , the 90% confidence intervals for the ratios of geometric least squared means of (R,S)-warfarin in combination with esopiclone to (R,S)-warfarin alone were lying between 80 and 125%. INR_{tmax} was not significantly different following (R,S)-warfarin in combination with esopiclone as compared to a single dose (R,S)-warfarin alone.

The effect of warfarin on esopiclone was not studied.

3.4.6 FOOD EFFECT-Study 190-002

To determine the effect of a high fat meal on the pharmacokinetics of single doses of (S)-zopiclone a study was done in healthy adult volunteers. The study used an oral solution. The study was done as a two-center, daytime administration, randomized, double blind, placebo-controlled, parallel-group, in-patient study in healthy male and female volunteers. There were two study periods. During Period 1, subjects were randomized to receive either placebo or one of three dose levels of (S)-zopiclone following a high fat breakfast. Period 2, subjects were dosed with the same dose as in Period 1 in the fasted state.

Table 17: (S)-Zopiclone pharmacokinetics with and without food

Parameter	Statistic	Single Dose			Single Dose			% Decrease Fed/Fasted	% Decrease Fed/Fasted	% Decrease Fed/Fasted
		Period 1, Day 1 (Fed)			Period 2, Day 1 (Fasted)					
		1 mg	3 mg	6 mg	1 mg	3 mg	6 mg			
C _{max} (ng/mL)	N	12	12	12	11	12	12			
	Mean	6.15	19.88	40.28	10.29	25.48	54.68	40	22	26
	SD	1.12	4.14	10.83	2.69	7.08	19.14			
t _{max} (hr)	N	12	12	12	11	12	12			
	Median	3.0	2.0	3.0	1.0	1.0	1.5			
	Range									
AUC _(0-inf) (ng*hr/mL)	n	10	12	12	11	12	12			
	Mean	58.24	183.02	368.27	62.85	195.74	406.67	7.3	6.4	9.4
	SD	14.08	50.57	98.14	15.71	64.37	120.81			
AUC ₍₀₋₂₄₎ (ng*hr/mL)	n	5	12	12	6	11	12			
	Mean	54.76	166.21	338.26	62.96	187.76	379.04			
	SD	8.06	49.03	90.10	8.42	49.75	110.25			

C_{max} levels for a 3 mg dose are lowered 22% by food whereas there was no effect of food on AUC. T_{max} was delayed by 1 hour with food.

3.4.7 ALCOHOL- Study 190-015

ALCOHOL INTERACTION WITH (S)-ZOPICLONE IN HEALTHY SUBJECTS

To determine the effects of esopiclone and alcohol during the daytime when administered alone and in combination on cognition and postural stability in healthy subjects.

This was a single center, inpatient, double-blind, randomized, 4-way crossover, placebo-controlled, single-dose study in normal healthy subjects. Twenty-four subjects were planned and enrolled.

Each sequence included four treatment regimens: A = placebo tablets plus alcohol placebo; B = placebo tablets plus alcohol, 0.7 g/kg; C = esopiclone, 3.5 mg plus alcohol placebo; and D = esopiclone, 3.5 mg, plus alcohol, 0.7 g/kg. The CDR (Cognitive drug research) system test battery was administered 1 hour pre-dose and 1, 2, 4, 8, and 12 hours post-dose on Study Day 1 and 24 hours post-dose on Study Day 2. There was a 7-day washout period between doses. A subject's total study participation was approximately seven weeks.

This study demonstrated that there was psychomotor performance impairment following co-administration of esopiclone and alcohol that was approximately additive. These effects were most apparent during the approximate period of peak drug effect (1-4 hours post dosing) and diminished with time.

3.5 INTRINSIC FACTORS- Study 190-005

What are the important in vivo intrinsic factors studied by the sponsor e.g., age, liver disease and renal disease

3.5.1 AGE

A 36 subject study compared (S)-zopiclone doses of 2.0 mg and 3.0 mg in individuals from ages 65-78 to (S)-zopiclone pharmacokinetics in young subjects.

Table 18. Summary statistics for a single dose of (S)-Zopiclone Pharmacokinetic Parameters Following Single and Multiple (7 day administration) Oral Doses of 3 mg (S)-Zopiclone in normals and in the elderly.

3 mg Single Dose

Parameter	Normals	Elderly	% Change Normal → Elderly
Cmax ng/ml	24.6(2.74)	29.50(8.20)	20 Increase
AUCinf ng/mlxhr	193.3(54)	296.02(103.72)	55 Increase
T1/2 hr	5.79(1.75)	9.05(2.39)	36 Increase

2 mg Single Dose

Parameter	Normals	Elderly	% Change Normal → Elderly
Cmax ng/ml	17.13(3.01)	15.32(3.37)	10 Decrease
AUCinf ng/mlxhr	118.7(18.6)	149.31(22.86)	26 Increase
T1/2 hr	5.53(1.64)	8.97(1.86)	62 Increase

3 mg Multiple Dose Day 7

Parameter	Normals	Elderly	% Change Normal → Elderly
Cmax ng/ml	26.18(6.56)	37.6(6.11)	45 Increase
AUC(0-tau) ng/mlxhr	191.07(60.88)	368.79(161.13)	93 Increase
T1/2 hr	7.03(4.00)	9.55(2.82)	36 Increase

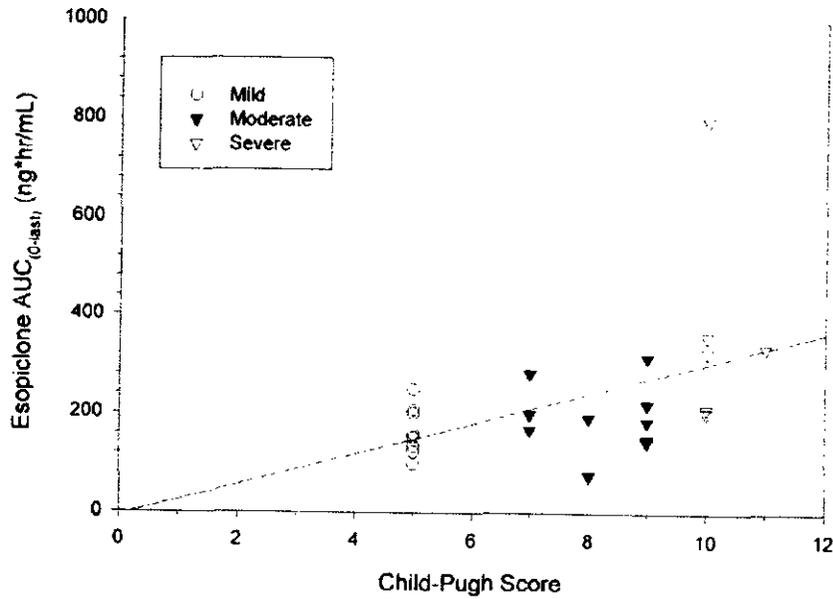
Following the 3 mg multiple dosing, the elderly AUC(0-tau) is twice normals and Cmax was increased by 45%. It appears that (S)-zopiclone clearance is reduced in the elderly. Therefore, the recommended dose for (S)-zopiclone in the elderly should be 2 mg.

3.5.2 LIVER DISEASE- Study 190-013

The study was done in 16 normals with each of 8 subjects in the mild, moderate and severe liver disease groups receiving 2 mg of (S)-zopiclone. Mean Child-Pugh classification for the hepatic groups were 5.0, 8.0 and 10 respectively.

Table 19: Mean ±SD Pharmacokinetic Parameters of Esopiclone Following Oral Administration of 2 mg of Esopiclone in Normal Subjects and Subjects with Mild, Moderate, and Severe Hepatic Impairment

Parameter	Hepatic Function Group				Per cent change Normal → Severe
	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)	
C _{max} (ng/mL)	25.1 ± 8.0	23.0 ± 7.0	20.6 ± 6.7	20.5 ± 9.3	18.3 Decrease
AUC(0-last) (ng h/mL)	172.2 ± 72.2	165.0 ± 50.1	195.2 ± 75.6	325.6 ± 204.8	89 Increase
AUC(0-inf) (ng h/mL)	188.1 ± 75.0	179.3 ± 50.5	221.4 ± 91.7 ^a	364.2 ± 209.0	94 Increase
t _{1/2} (h)	6.66 ± 2.14	6.79 ± 1.75	11.05 ± 5.64 ^a	15.34 ± 6.06	130 Increase
Urine recovery %	5.69 ± 1.64	7.43 ± 4.01	5.78 ± 3.72	6.96 ± 4.34	
^a N=7					



Further analysis of the regression of AUC(0-t) was done following elimination of the subject with a severe classification and AUC(0-t) of 797 ng/mlxhr. The resulting regression equations for Child-Pugh Score vs AUC(0-t) were:

	Slope	Intercept	Rsq
AUC(0-t)-All Data	28.09	14.39	0.20
AUC(0-t)> 500 deleted	17.85	74.85	0.25
Cmax	-0.31	23.70	0.008

Deletion of this subject primarily impacted the intercept resulting in a large change in predicted AUC (0-t) values for subjects with lower Child-Pugh Scores. Subjects with mild and moderate Child-Pugh Scores were comparable to normals whereas subjects classified as severe had AUC and half-life values twice those observed in normals.

Therefore subjects with severe liver damage should only receive the lower 2 mg dose of esopiclone with caution since their exposure level would be comparable to a 4 mg dose in normals.

3.5.3 RENAL DISEASE-Study 190-014

The study was done as a multicenter, inpatient, open-label, single-dose study in subjects with renal impairment (mild, moderate, or severe) and gender-, age-, height- and weight-matched healthy subjects. The study was done in 40 subjects. Subjects were classified into renal function groups by urine creatinine clearance test results.

The following table summarizes the mean baseline creatinine clearance by renal function group.

Group	Creatinine Clearance (mL/min)
1 (normal)	> 80
2 (mild)	>50 < 80
3 (moderate)	>30 <50
4 (severe)	< 30

Table 20: Mean \pm SD Pharmacokinetic Parameters of (S)-zopiclone Following Oral Administration of 3.0 mg (S)-zopiclone in Normal Subjects and Subjects with Mild, Moderate and Severe Renal Impairment

Parameter	Renal Function Group				Per cent Change Normal \rightarrow Severe
	Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	

C_{max}					
(ng/mL)	36.7 ± 11.4	43.1 ± 10.6	32.4 ± 7.8	43.4 ± 15.4	18
AUC _(0-last)					
(ng hr/mL)	271.0 ± 87.3	372.3 ± 118.2	304.7 ± 77.8	385.6 ± 139.4	42
AUC _(0-∞)					
(ng hr/mL)	284.5 ± 91.4	388.3 ± 119.6	319.1 ± 78.5	400.8 ± 141.6	41
$t_{1/2}$					
(hr)	6.12 ± 1.94	7.30 ± 1.09	7.60 ± 1.66	8.16 ± 2.59	22
t_{max}^a	1.25	1.00	1.00	1.00	
(hr)					
Cl _r					
(L/hr)	0.811 ± 0.471 ^b	0.564 ± 0.593	0.614 ± 0.440	0.496 ± 0.396	
Recovery%	6.76 ± 3.53 ^c	6.75 ± 6.65	5.91 ± 3.81	4.92 ± 2.13	
a expressed as median [range].					
b n=14					
c n=15					

Since only 6% of an administered dose is excreted unchanged in the urine, results from the renal factor studies indicated that there is no adjustment required for subjects with severe renal impairment

3.5.4 Meta Analysis -Study 190-000-K01

The primary objective of these analyses was to evaluate the effect of age, race, gender, and weight on exposure (C_{max} and AUC) to (S)-zopiclone following single and multiple dosing. Data from 11 phase I studies presented in this NDA were combined and analyzed.

The modeling process included the selection of a statistical base model, expansion of the base model by step-wise selection of covariates ("step-up" procedure), refinement of this full model by step-wise deletion of non-significant terms ("step-down" procedure), assessment of interactions, and establishment of a final model. The same modeling process was utilized for single-dose and steady-state AUC and C_{max} dependent variables. Once the modeling process was completed, the effect of each demographic variable in the final model on exposure to esopiclone was evaluated.

In addition, a supplemental analysis was carried out to further investigate age effects. This supplemental assessment of the effect of age on exposure was carried out by comparing demographically matched elderly subjects with non-elderly controls.

The only demographic variable with a substantial effect on exposure was age. The multiple dose findings of the different analyses with respect to age group are summarized in the following Table.

Product Administered:

- A = Liquid (S)-zopiclone, 3.5 mg single dose;
- B = Tablet (S)-zopiclone, 3.5 mg daily for 4 days (2x1.0 mg and 1x1.5mg);
- C = Tablet racemic zopiclone (Imovane), 7.5 mg daily for 4 days

S-zopiclone was measured for all formulations administered.

The relative BA was 1.00 (tablet/liquid) following single and multiple dosing for AUC(0-t) and Cmax. Also the (S)-zopiclone tablet is BE to the (S)-zopiclone solution.

3.6.2 BIOEQUIVALENCE OF CLINICAL VS TO-BE- MARKETED FORMULATION- Study 190-011

This was a two-center, in-patient, randomized, two-way cross-over (within a group), open-label, single dose study in healthy adults. Subjects in Group A received, in random sequence, a 2 mg single oral dose of esopiclone clinical service formulation tablet (2x 1mg) and a 2 mg single oral dose of the intended-for-market formulation tablet. Subjects in Group B received, in random sequence, a 3 mg, single oral dose of esopiclone clinical service formulation tablet (2x1.5 mg) and a 3 mg, single oral dose of the intended-for-market formulation tablet. There were 20 enrolled in each study group.

The 3 mg to-be-marketed tablet was BE to 2x1.5 mg of the clinically studied tablet and the 2 mg to-be-marketed was BE to 2x1.0 mg of the clinically studied tablet.

3.6.2.1 Formulation Information:

Table 21: Composition of Eszopiclone Investigational Tablet Formulations

Component	Amount (mg/tablet)			
	1.0 mg Strength	1.5 mg Strength	2.0 mg Strength ^c	3.0 mg Strength ^c
Eszopiclone	1.0	1.5	2.0	3.0
Microcrystalline Cellulose NF				
Calcium Phosphate ISP				
Croscarmellose Sodium NF				
Colloidal Silicon Dioxide NF				
Magnesium Stearate NF				

blue^a

--- not applicable

^a Further information regarding the coating materials is provided in Section 4.A.3.2 Inactive Components.

^c corresponds exactly to the proposed commercial product.

3.6.2.2 Dissolution Data

1. The dosage form dissolution characteristics were evaluated over the pH range of ... Accordingly, a single-point dissolution acceptance criterion at a lower limit is warranted.
2. Thus, subsequent evaluation was based exclusively upon dissolution data at pH
3. Dissolution conditions and specifications are presented in the following table.

Summary of Drug Product Dissolution Method and Specification	
Dosage Form	Eszopiclone Tablets
Strengths	2.0 and 3.0 mg
Apparatus	USP Type 2 apparatus (paddle)
Media	
Volume	
Speed of Rotation	
Sampling Time(s)	5, 10, 20, 30, and 45 minutes
Brief Description of the Dissolution Method	
Recommended Dissolution Acceptance Criterion	Conforms to USP <711>, Apparatus 2 Q= at 30 minutes

The dissolution profile for the 2 mg batch(F0468003) and the 3 mg batch (F0548002) used in the pivotal BE studies were developed using these conditions and the data are presented in the Appendix.

Based on the data provided, the firm's proposed dissolution method and specification are acceptable to OCPB.

3.7 ANALYTICAL

What is the analytical methodology and is the method sufficiently robust to support the data presented.

Parameter	(S)-Zopiclone	(R-)&(S-)Zopiclone		Zopiclone
Method	LC/MS/MS	LC/MS/MS		LC/MS/MS
Freeze-thaw	—	—		—
Benchtop Stability at RT	—	—		—
Long term at -20° C	—	—		—
Recovery	Parent	R-Parent	S-Parent	RS-Parent
Low				
Med	/	/	/	/
High				

The analytical method can analyze — of (S) zopiclone in plasma and is acceptable.

What analytical methods were used and were they acceptable?

Several different analytical methods were used:

Analyte	Method	Assay Sensitivity ng/ml
Zopiclone	LC/MS/MS	
Ketaconazole	/	/
(R,S)Warfarin		
Digoxin	Immunoassay	
Olanzapine		
Lorazepam	/	/
Paroxetine		

4.0 LABELING

4.1 OCPB LABELING

ESTORRA™ (eszopiclone) TABLETS 3 mg, 2 mg

5.0 SIGNATURES

Andre Jackson _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

Cc-NDA 21476, HFD-860 (Jackson, Baweja, Sahajwalla, Mehta),
Central Documents Room (Biopharm-CDR)

OCPE Briefing September 23, 2003 (Jackson, Baweja, Sahajwalla,
Mehta, Lazor, Andreason, Malinowski)

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6.0 APPENDIX

6.1 NDA ASSAY VALIDATION-Plasma¹

Parameter	(s)-Zopiclone	(R-)Zopiclone	Zopiclone
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Freeze-thaw	—	—	—
Benchtop Stability at RT	—	—	—
Long term at -20° C	—	—	—
Recovery	S-Parent	R-Parent	RS-Parent
Low	/	/	/
Med	/	/	/
High	/	/	/

1.Validation data for metabolites s-desmethylzopiclone and N-oxide-zopiclone were not presented although analyzed by the firm since they were both inactive

6.2 NDA ASSAY VALIDATION-Urine

Parameter	Zopiclone
Method	LC/MS/MS
Freeze-thaw	—
Benchtop Stability at RT	—
Long term at -80° C	—

Recovery	RS-Parent
Low	
Med	
High	

6.3 PHARMACOKINETIC STUDIES

6.3.1 Individual Study Report- Study 190-010-Relative Bioavailability of Two Formulations for S-Zopiclone and Imovane in Healthy Subjects

Study Introduction and Objectives

(S)-Zopiclone has previously been administered in a liquid formulation. Because Sepracor Inc. was interested in developing (S)-zopiclone in a tablet formulation and demonstrating that (R)-zopiclone has little or no effect upon the metabolism of (S)-zopiclone or its primary metabolites, the current bioavailability study (190-010) was conducted

STUDY OBJECTIVES

- To compare the pharmacokinetic profiles of (S)-zopiclone and its metabolites following daytime oral administration of liquid and tablet (S)-zopiclone 3.5 mg and tablet racemic zopiclone (Imovane[®]) 7.5 mg.
- To establish the relative bioequivalence between single doses of the liquid and tablet formulations of (S)-zopiclone 3.5 mg.

Study Design

This was a single-center, inpatient, single-dose and multiple-dose, three period complete crossover, random sequence, open-label study in 18 healthy males and females between the ages of 21 and 45 years, inclusive. Subjects were enrolled in two groups of nine. A subject's participation involved four visits: a screening visit plus three multiple-day inpatient visits.

Product Administered:

- A = Liquid (S)-zopiclone, 3.5 mg single dose;
- B = Tablet (S)-zopiclone, 3.5 mg daily for 4 days ;
- C = Tablet racemic zopiclone, 7.5 mg daily for 4 days

Demographics

Table 1A Demographic and Baseline Characteristics For All Subjects And By Treatment Sequence

Characteristic	All Subjects	ABC	ACB	BAC	BCA	CAB	CBA
----------------	--------------	-----	-----	-----	-----	-----	-----

	(N=18)	(N=3)	(N=3)	(N=3)	(N=3)	(N=3)	(N=3)
Age (yrs)							
N	18	3	3	3	3	3	3
Mean	30.4	34.0	29.0	29.7	29.7	28.7	31.7
SD	7.8	10.5	6.1	11.0	10.3	1.5	10.3
Gender N(%)							
Male	13 (72%)	3 (100%)	2 (67%)	3 (100%)	3 (100%)	2 (67%)	0
Female	5 (28%)	0	1 (33%)	0	0	1 (33%)	3 (100%)
Race N(%)							
Caucasian	9 (50%)	2 (67%)	2 (67%)	2 (67%)	2 (67%)	0	1 (33%)
Black	6 (33%)	1 (33%)	1 (33%)	0	1 (33%)	3 (100%)	0
Asian	1 (6%)	0	0	0	0	0	1 (33%)
Hispanic	1 (6%)	0	0	1 (33%)	0	0	0
Other	1 (6%)	0	0	0	0	0	1 (33%)
Height (cm)							
N	18	3	3	3	3	3	3
Mean	174	179.1	169.0	178.3	178.7	179.7	159.0
SD	9.3	3.9	6.0	7.0	4.5	8.4	5.2
Median	175.2	179.0	169.0	178.0	180.5	181.5	161.5
Min	153	175	163	172	174	171	153
	187	183	175	186	182	187	163
Weight (kg)							
N	18	3	3	3	3	3	3
Mean	75.8	84.9	67.8	77.7	90.5	76.3	57.6
SD	13.4	7.2	5.9	11.6	6.2	9.9	11.2

Eighteen subjects were randomized to receive one of the six possible treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA) over three periods (Visits 2, 3, and 4), with the treatments defined as follows: A = Liquid (S)-zopiclone, 3.5 mg single dose; B = Tablet (S)-zopiclone, 3.5 mg daily for 4 days ; C = Tablet racemic zopiclone, 7.5 mg daily for 4 days

Sample Collection and Handling

Day 1

Post-Dose -Obtained a blood sample (5 mL) for plasma zopiclone levels at +30 minutes, +60 minutes, +90 minutes, +2 hours, +3 hours, +4 hours, +6 hours, +8 hours, +12 hours and +16 hours.

Day 4

Obtained a blood sample (5 mL) for plasma zopiclone levels at -15 minutes.

Post-Dose - Obtained a blood sample (5 mL) for plasma zopiclone levels at +30 minutes, +60 minutes, +90 minutes, +2 hours, +3 hours, +4 hours, +6 hours, +8 hours, +12 hours and +16 hours.

Day 5

The following procedures were performed relative to the time of dosing on Day 4.

Obtained a blood sample (5 mL) for plasma zopiclone levels at +24 hours, +30 hours and +36 hours.

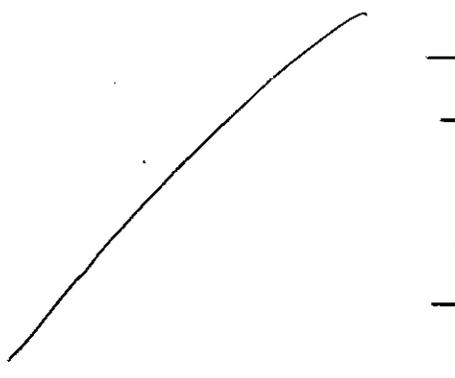
Bioanalytical Methods

Studied Period (years): Clinical Conduct : June 28, 2000 – September 11, 2000

Analysis of plasma samples was conducted from

Theoretical Storage time:

Parameter	S(+)-Zopiclone	R(-)-Zopiclone
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	— ng/mL	— ng/mL
Linearity (Standard curve samples)	— ng/mL	— ng/mL
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		



Statistical Analysis

For each analyte, the following PK parameters were determined after a single dose administration (Day 1) of the liquid and tablet formulation of (S)-zopiclone, and tablet formulation of racemic zopiclone:

Single Dosing Parameters

C _{max} – Maximum observed concentration.	T _{max} – Time of occurrence of C _{max} .	C _{last} – The last post-dose quantifiable concentration.	t _{last} – The time of the last post-dose quantifiable concentration.
k – Elimination rate constant	t _{1/2} – Terminal half-life, calculated as ln(2)/k.	AUC(0-last) Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration	AUC(0-inf) Area under the plasma concentration-time curve for the 0-infinity

C_{last} / k is the extrapolated area under the curve from t_{last} to infinity. If this quantity was greater than 30% of AUC(0-inf), then AUC(0-inf) was to be considered to be missing.

For each analyte, the following PK parameters were determined after multiple dose administration (Day 4) of the tablet formulation of (S)-zopiclone and racemic zopiclone: Cmax, tmax, Clast, tlast,lz, t½, AUC(0-last), and AUC(0-inf) as defined above.

<p>•• Nominal dosing interval.</p>	<p>AUC(0-∞)- Area under the plasma concentration time curve over the dosing interval (t), calculated using the linear trapezoidal rule, based on actual sample times</p>	<p>R -Cmax -- Ratio of Cmax on the last and first day of the multiple dosing regimen, RCmax = Cmax(4) / Cmax(1), where 1 and 4 refer to the first (Day 1) and last (Day 4) days of drug administration.</p>
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R AUC - RAUC = AUC(0-∞)(4) / AUC(0-∞)(1), where 1 and 4 refer to the first (Day 1) and last (Day 4) days of drug administration.

For the analyte (S)-zopiclone AUC(0-∞) and Cmax values for tablet (S)-zopiclone were dose adjusted through multiplication by 1.07 (3.75/3.5) prior to comparison with racemic zopiclone. These dose adjustments were made for use in assessing bioequivalence only (since the racemic dose for (S)-zopiclone was 7.5 mg/2=3.75), and not applied to descriptive statistics for PK parameters. The analyses were conducted using an analysis of variance (ANOVA) model with treatment, sequence, period, and first-order carryover as fixed effects, and subject nested within sequence as a random effect. The analyses were performed after transformation of the data using the natural logarithm (loge). A test for first-order carryover effect was conducted at the 5% significance level. If the test was not statistically significant, the first-order carryover effect terms was dropped from the model for the final analysis. The log-transformed results were transformed back to the original scale by exponentiation to obtain geometric least squares means for each treatment. Two one-sided hypothesis tests at the 0.05 level of significance were performed by constructing 90% confidence intervals (CI) on the ratio of the geometric means for the treatment comparisons mentioned above.

RESULTS

Table 2A (S)-Zopiclone PK Parameters Following Administration of Liquid and Tablet (S)-Zopiclone and Tablet Racemic Zopiclone

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Parameter	Stat	Liquid (S)-Zopiclone		Tablet (S)-Zopiclone		Imovane® Tablet	
		Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
C_{max} (ng/mL)	N	15	16	16	17	17	17
	Mean	29.57	32.94	33.39	33.78	35.58	35.58
	Std Dev	9.02	13.62	14.56	7.61	9.70	9.70
$AUC_{(0-t)}$ (hr*ng/mL)	N	15	16	15	17	17	17
	Mean	190.18	196.61	227.40	225.79	252.41	252.41
	Std Dev	49.41	60.54	80.07	60.95	47.95	47.95
$t_{1/2}$ (hr)	N	15	16	16	17	17	17
	Mean	6.27	5.86	7.02	6.76	8.27	8.27
	Std Dev	1.91	1.76	2.35	1.78	4.00	4.00
t_{max} (hr)	N	15	16	16	17	17	17
	Median	1.00	1.00	1.00	1.50	1.50	1.50
	Range						
$R_{C_{max}}$	N	NA	NA	16	NA	17	17
	Mean	NA	NA	1.09	NA	1.12	1.12
	Std Dev	NA	NA	0.49	NA	0.47	0.47
R_{AUC}	N	NA	NA	15	NA	17	17
	Mean	NA	NA	1.15	NA	1.10	1.10
	Std Dev	NA	NA	0.11	NA	0.16	0.16

Note: Values were not dose adjusted.

Table 3A Relative Bioavailability Between Multiple Doses of the Tablet Formulations of (S)-Zopiclone and Racemic Zopiclone (Imovane).

Parameter ¹	Comparison	Tablet (S)-Zopiclone		Ratio	90% CI	P-Value ²
		Geometric LS Mean	Racemic Zopiclone Geometric LS Mean			
C_{max}	(S)-Zopiclone/Racemic Zopiclone	34.1	34.4	99.0	86.9, 112.8	0.8937
$AUC_{(0-t)}$	(S)-Zopiclone/Racemic Zopiclone	237.1	238.3	99.5	90.7, 109.1	0.9229
$t_{1/2}$	(S)-Zopiclone/Racemic Zopiclone	6.9	7.3	93.7	84.8, 103.4	0.2631
t_{max} ³	(S)-Zopiclone/Racemic Zopiclone	1.0	1.5	0.0585
$R_{C_{max}}$	(S)-Zopiclone/Racemic Zopiclone	1.2	1.1	105.8	99.6, 112.4	0.1227
R_{AUC}	(S)-Zopiclone/Racemic Zopiclone	1.0	1.0	96.8	79.1, 118.0	0.7735

¹ Units: $AUC_{(0-t)}$ is measured in ng*hr/mL, C_{max} in ng/mL, and $t_{1/2}$ and t_{max} in hr.

² Ratio (%) of geometric means (LS Means) for the log-transformed analysis.

³ P-value for treatment effect from the ANOVA model.

⁴ Values of t_{max} were rank-transformed prior to the analysis and the medians of the original values were reported for the treatments.

Note: Values were dose adjusted per Section 9.7.2.2

Table 4A Relative Bioavailability Between Single Doses of the Liquid and Tablet Formulations of (S)-Zopiclone

Analyte	Parameter [1]	90% CI
(S)-zopiclone	C _{max}	(94.3, 124.5)
	AUC(0-t)	(92.5, 109.6)

Comments:

1. Based upon the 90% CI for R_{AUC} and R_{C_{max}} there appeared to be little accumulation in normals.

2. The tablet formulation of S-Zopiclone had a relative bioavailability (i.e., F_{tablet}/F_{solution}) of 1.03 compared to the liquid.

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6.3.2 Individual Study Report- Study 190-011 -BE STUDY BETWEEN CLINICAL AND TO-BE-MARKETED PRODUCTS

Study Introduction and Objectives

This trial was conducted to establish the bioequivalence between single doses of the clinical service formulation tablets (2 mg and 3 mg) of esopiclone and the intended-for-market formulation tablet (2 mg and 3 mg, respectively) of esopiclone.

STUDY OBJECTIVES

The objectives were:

- 1.To establish the bioequivalence between single doses of the 2 mg clinical service formulation tablet of esopiclone and the 2 mg (batch #F0468003) intended-for-market formulation tablet of esopiclone.
- 2.To establish the bioequivalence between single doses of the 3 mg clinical service formulation tablet of esopiclone and the 3 mg (batch # F0548002) intended-for-market formulation tablet of esopiclone.

Study Design

This was a two-center, in-patient, randomized, two-way cross-over (within a group), open-label, single dose study in healthy adults. Subjects were in 1 of 2 groups (A or B). Group A was at one investigator site and Group B was at another investigator site. Subjects in Group A received, in random sequence, a 2 mg single oral dose of esopiclone clinical service formulation tablet and a 2 mg single oral dose of the intended-for-market formulation tablet. Subjects in Group B received, in random sequence, a 3 mg, single oral dose of esopiclone clinical service formulation tablet and a 3 mg, single oral dose of the intended-for-market formulation tablet. Subjects were assigned to receive one of the following two treatments during each treatment period in a randomized cross-over fashion.

Treatment Period 1: Group A: A single oral dose of 2 mg clinical service tablets (2 x 1 mg tablets) administered under fasted conditions. Group B: A single oral dose of 3 mg clinical service tablets (2 x 1.5 mg tablets) administered under fasted conditions.

Treatment Period 2: Group A: A single oral dose of 2 mg intended-for-market formulation tablets (1 x 2 mg tablets) administered under fasted conditions. Group B: A single oral dose of 3 mg intended-for-market formulation tablets (1 x 3 mg tablet) administered under fasted conditions.

Demographics

Table 5A Demographic and Baseline Characteristics (Safety Population)

Characteristic	Statistic	Treatment Sequence ^a				All Subjects (n=79)
		I/II (n=20)	II/I (n=20)	III/IV (n=20)	IV/III (n=19)	
Age	Mean (yr)	42.8	39.4	42.5	30.6	38.9
	SD (yr)	15.3	13.0	16.9	13.7	15.3
	Min. Max	20, 62	19, 64	21, 64	21, 59	19, 64
Gender						
Male	n (%)	12 (60.0)	11 (55.0)	9 (45.0)	8 (42.1)	40 (50.6)
Female	n (%)	8 (40.0)	9 (45.0)	11 (55.0)	11 (57.9)	39 (49.4)
Race						
Caucasian	n (%)	16 (80.0)	15 (75.0)	19 (95.0)	18 (94.7)	68 (86.1)
Black	n (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Asian	n (%)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	2 (2.5)
Hispanic	n (%)	3 (15.0)	3 (15.0)	0 (0.0)	1 (5.3)	7 (8.9)
Other	n (%)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)

Sample Collection and Handling

A blood sample for pharmacokinetic assessments was obtained at +0.50 hr, +1 hr, +1.5 hr, +2 hr, +3 hr, +4 hr, +6 hr, +8 hr, +12 hr and +16 hr post dose

Bioanalytical Methods-

Parameter	Zopiclone
Method	LC/MS/MS
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Studied Period (years): Clinical Conduct March 19, 2001 to May 21, 2001
 Analysis of plasma samples was conducted from _____
 Theoretical Storage time: _____

Statistical Analysis

The following PK parameters were determined after a single dose administration of 2 mg and or 3 mg to-be-marketed tablet formulations.

C _{max} – Maximum observed concentration.	T _{max} – Time of occurrence of C _{max} .	C _{last} – The last post-dose quantifiable concentration.	t _{last} - The time of the last post-dose quantifiable concentration.
k – Elimination rate constant	t _{1/2} - Terminal half-life, calculated as ln(2)/k.	AUC(0-last) Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration	AUC(0-inf) Area under the plasma concentration-time curve for the 0-infinity

C_{last} / k is the extrapolated area under the curve from t_{last} to infinity. If this quantity was greater than 30% of AUC(0-inf), then AUC(0-inf) was to be considered to be missing.

RESULTS

Table 6A Mean Plasma Concentrations of Esopiclone Following Treatment with a Single 2 mg Dose of Esopiclone as a Clinical Service Formulation (CSF) or an Intended-For-Market Formulation (IMF)

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Day	Time (hr)	N	E.sopiclone concentration (ng/ml)			
			Clinical Service Formulation		Intended-For-Market Formulation	
			Mean	SD	Mean	SD
1	Pre-dose	40	BLQ	-	BLQ	-
	0.5	40	12.54	9.13	18.58	10.30
	1	40	19.87	5.87	22.41	5.54
	1.5	40	19.83	4.67	20.76	4.04
	2	40	18.63	3.82	19.37	4.04
	3	40	16.46	2.94	16.58	3.30
	4	40	14.52	2.75	14.69	3.00
	6	40	10.73	2.48	10.55	2.08
	8	40	8.17	2.19	8.44	2.02
	12	40	4.59	1.58	4.86	1.54
	16	40	2.92	1.45	2.93	1.29
2	24	40	BLQ	-	1.11	1.00

BLQ: Below limit of quantification (-)

Table 7A Mean \pm SD Pharmacokinetic Parameters of Esopiclone Administered as a Single 2 mg Dose as CSF or IMF

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Parameter	Mean ± SD			
	N	Clinical Service Formulation	N	Intended-For-Market Formulation
C_{max} (ng/ml)	40	22.45 ± 5.59	40	25.10 ± 6.98
$AUC_{(0-last)}$ (hr*ng/ml)	40	160.98 ± 42.08	40	168.95 ± 42.80
$AUC_{(0-∞)}$ (hr*ng/ml)	40	176.02 ± 46.64	40	184.94 ± 47.51
$t_{1/2}$ (hr)	40	5.51 ± 1.38	40	5.73 ± 1.48
t_{max}^a (hr)	40	1.00 (—)	40	1.00 (—)

^a expressed as median (range)

Table 8A Statistical Treatment Comparison of Esopiclone Pharmacokinetic Parameters (Single 2 mg Dose)

Parameter	Treatment	LSMean	Ratio (%) (T/R)	90% CI
C_{max}	Clinical Service Formulation	21.9		
	Intended-for-Market Formulation	24.2	110.8	(103.9, 118.2)
$AUC_{(0-last)}$	Clinical Service Formulation	155.6		
	Intended-for-Market Formulation	163.4	105.0	(100.0, 110.3)
$t_{1/2}$	Clinical Service Formulation	5.3		
	Intended-for-Market Formulation	5.5	103.8	(99.8, 108.0)
t_{max}	Clinical Service Formulation	1.0		
	Intended-for-Market Formulation	1.0	-	-
$AUC_{(0-inf)}$	Clinical Service Formulation	170.0		
	Intended-for-Market Formulation	178.6	105.1	(100.5, 109.8)

Table 9A Mean Plasma Concentrations of Esopiclone Following Treatment with a Single 3 mg Dose of Esopiclone as a Clinical Service Formulation (CSF) or an Intended-For-Market Formulation (IMF)

Day	Time (hr)	N	Esopiclone concentration (ng/ml)			
			Clinical Service Formulation		Intended-For-Market Formulation	
			Mean	SD	Mean	SD
1	Pre-dose	39	BLQ	-	BLQ	-
	0.5	39	28.45	15.51	26.32	11.66
	1	39	36.85	12.55	38.76	10.92
	1.5	39	36.36	11.72	36.40	10.38
	2	39	34.77	9.81	34.25	10.60
	3	39	29.71	8.64	30.54	8.68
	4	39	25.46	6.84	26.18	8.10
	6	39	19.40	4.75	18.85	5.91
	8	39	14.94	4.22	14.97	5.30
	12	39	8.91	3.40	8.45	3.18
	16	39	5.65	2.60	5.11	2.08
2	24	39	2.46	1.69	2.28	1.32

BLQ: Below limit of quantification

Table 10A Mean ± SD Pharmacokinetic Parameters of Esopiclone Administered as a Single 3 mg Dose as CSF or IMF

Appears This Way
On Original

Parameter	Mean ± SD			
	N	Clinical Service Formulation	N	Intended-For-Market Formulation
C_{max} (ng/ml)	39	43.69 ± 11.41	39	43.16 ± 10.22
$AUC_{(0-last)}$ (hr*ng/ml)	39	305.98 ± 80.65	39	301.11 ± 83.44
$AUC_{(0-inf)}$ (hr*ng/ml)	39	334.95 ± 100.10	39	324.68 ± 91.18
$t_{1/2}$ (hr)	39	6.12 ± 1.48	39	5.98 ± 1.16
t_{max}^a (hr)	39	1.00 / —	39	1.00 / —

^a expressed as median (range)

Table 11A: Statistical Treatment Comparison of Esopiclone Pharmacokinetic Parameters (Single 3 mg Dose)

	Treatment	LSMean	Ratio (%) (T/R)	90% CI
C_{max}	Clinical Service Formulation	42.1		
	Intended-for-Market Formulation	42.1	100.1	(90.8, 110.2)
$AUC_{(0-last)}$	Clinical Service Formulation	295.0		
	Intended-for-Market Formulation	291.1	98.7	(90.1, 108.1)
$t_{1/2}$	Clinical Service Formulation	5.9		
	Intended-for-Market Formulation	5.9	98.6	(95.0, 102.4)
t_{max}	Clinical Service Formulation	1.0		
	Intended-for-Market Formulation	1.0	-	-
$AUC_{(0-inf)}$	Clinical Service Formulation	320.0		
	Intended-for-Market Formulation	313.5	98.0	(89.3, 107.4)

Comments:

1. The to-be-marketed 2 mg and 3 mg tablets are BE to the clinical service formulations at 2x1.0 mg and 2x1.5 mg respectively.

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6.3.3 MASS BALANCE STUDY-RPR ZD-0008
Individual Study Report-

Study of the metabolism of zopiclone (27.267 R.P.) and the elimination of radiolabelled products in man following a single oral dose (7.5 mg) of ^{14}C -zopiclone.

Objectives

Results

Blood and plasma

The concentrations of zopiclone in whole blood reached maximum from 15 min. to 3 hours. The peak concentration was 79.9 ± 21.2 ng - eq./ml.

The mean maximum concentration for plasma was 103.3 ± 24.0 ng - eq./ml.

The T_{max} varied from — , with a mean of 1.7 hours.

The mean blood to plasma ratio was 0.82 ± 0.04

The mean AUC value in blood was 1780 ± 678 ng/ml-h and for plasma 2111 ± 503 ng/ml-h.

The results are summarized in table 1.

Table 1

Mean values for the parameters calculated from total radioactivity

	Blood	Plasma
C_{max}	79.9 ng/ml	103.3 ng/ml
T_{max}	1.9 h	1.7 h
AUC	1780 ng/ml-h	2111 ng/ml-h
$T_{1/2}$	58.4 h	54.0 h

Expired air

The radioactivity of expired air for the two subjects (0-48 h) was as follows:

Subject 1: — equal to 0.48% of the dose administered

Subject 2: — equal to 0.06% of the dose administered

Urine

The mean amount of zopiclone excreted into urine during 120 hours was $74.8 \pm 9.3\%$ (5.5 ± 0.7 mg - equivalent zopiclone) of the total dose administered.

Faeces

The mean total recovery of radioactivity in the faeces was 15.8 ± 2.8% (1.2 ± 0.2 - equivalent zopiclone) of the total dose administered.

Conclusions

The authors conclude the following: The study provided useful information on total radioactivity of zopiclone in blood and plasma and on the elimination of the radioactivity in urine and faeces after a single dose of 7.5 mg.

It confirms that the size of biological samples was large enough to allow metabolism of the drug to be followed.

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6.3.4 Individual Study Report- Study 190-001-A DAYTIME, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE DOSE-RISING SAFETY AND PHARMACOKINETIC STUDY OF (S)-ZOPICLONE IN HEALTHY VOLUNTEERS

Study Introduction and Objectives

The current study was designed to determine the safety and tolerability of (S)-zopiclone. It also determined the pharmacokinetic (PK) profile of (S)-zopiclone alone, the PK profile of (S)-zopiclone with the presence of (RS)-zopiclone, and the pharmacodynamic (PD) profiles of (S)-zopiclone, (RS)-zopiclone, and zolpidem.

PRIMARY AND SECONDARY OBJECTIVES

- To determine the safety and tolerability of single escalating doses of (S)-zopiclone compared to placebo in healthy adult volunteers.
- To determine the PK profile of single escalating doses of (S)-zopiclone in healthy volunteers.
- To determine the PK profile of (S)-zopiclone in the presence of (R)-zopiclone.

Study Design

The dosage form used in this study was an oral solution. This was a single-center, daytime, randomized, double-blind, placebo-controlled, single dose escalation, in-patient study in healthy male and female subjects. Doses evaluated included 1.0, 2.0, 2.5, 3.0, 3.75, 5.0, and 7.5 mg of (S)-zopiclone, 5 and 10 mg of zolpidem, and 2.5, 5.0, and 7.5 mg of (RS)-zopiclone. Dose escalation in (S)-zopiclone was accomplished by evaluating sequential panels of nine subjects each, six of whom were randomized to receive active drug or, in the case of the 7.5 mg (S)-zopiclone panel, 15 subjects, 10 of whom were randomized to receive active drug. If a dose showed dose-limiting toxicity, the higher doses were not to be studied. Racemic zopiclone was included to compare the PK profiles and an active control, zolpidem was included as a reference.

Demographics

			Demographic and Baseline Characteristics					
			Part 1 of 2					
			All Subjects Who Received Study Drug					
			(S)-Zopiclone Panels					
			1.0 mg	2.0 mg	2.5 mg	3.0 mg	3.75 mg	5.0 mg
Characteristic	Treatment	Statistic	Active : (N=6)	(N=6)	(N=6)	(N=6)	(N=6)	(N=6)
			Placebo: (N=3)	(N=3)	(N=3)	(N=3)	(N=3)	(N=3)
Age (yrs)	Active	n	6	6	6	6	6	6
		Mean	28.8	25.3	32.3	23.7	28.7	26.3
		Std Dev	8.6	6.7	7.9	8.2	8.7	5.2
	Placebo	n	3	3	3	3	3	3
		Mean	24.3	34.3	23.3	30.7	32.3	28.0
		Std Dev	5.0	4.0	4.5	13.2	11.7	2.6
Gender								

Female	Active	n (%)	2 (33%)	2 (33%)	3 (50%)	2 (33%)	3 (50%)	2 (33%)
Male		n (%)	4 (67%)	4 (67%)	3 (50%)	4 (67%)	3 (50%)	4 (67%)
Female	Placebo	n (%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)	0
Male		n (%)	2 (67%)	2 (67%)	2 (67%)	2 (67%)	2 (67%)	3 (100%)
Ethnic Origin								
Asian	Active	n (%)	0	0	0	0	0	1 (17%)
Black		n (%)	1 (17%)	3 (50%)	2 (33%)	1 (17%)	2 (33%)	0
Caucasian		n (%)	5 (83%)	3 (50%)	3 (50%)	5 (83%)	4 (67%)	4 (67%)
Hispanic		n (%)	0	0	1 (17%)	0	0	1 (17%)
Native American		n (%)	0	0	0	0	0	0
Other		n (%)	0	0	0	0	0	0
Asian	Placebo	n (%)	0	0	0	0	0	0
Black		n (%)	0	0	1 (33%)	0	0	0
Caucasian		n (%)	3 (100%)	3 (100%)	2 (67%)	3 (100%)	3 (100%)	3 (100%)
Hispanic		n (%)	0	0	0	0	0	0
Native American		n (%)	0	0	0	0	0	0
Other		n (%)	0	0	0	0	0	0

Sample Collection and Handling

Samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 30, 36, and 48 hours.

Bioanalytical Methods-

Studied Period (years): Clinical Conduct August 22, 1999-December 22, 1999

Analysis of plasma samples was conducted from

Theoretical Storage time:

Parameter	S(+)-Zopiclone	R(-)-Zopiclone
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		

Statistical Analysis

The following pharmacokinetic parameters were estimated for each analyte: the peak concentration (C_{max}), time to reach the peak concentration (t_{max}), the terminal rate constant (λ_z), the terminal half-life ($t_{1/2}$), the area under the concentration-time curve from zero to the last measurable time point (AUC_{last}), the area under the concentration-time curve from zero to infinity (AUC_{inf}), and the fraction of AUC_{inf} due to extrapolation (AUC_{ext}).

Descriptive statistics (number of subjects, mean, median, standard deviation, minimum, maximum, and %CV) of PK parameters were computed separately by dose group and treatment [(S)-zopiclone and (RS)-zopiclone]. PK parameter ratios of (S)-zopiclone to (R)-zopiclone were determined for subjects receiving oral administration of (RS)-zopiclone. Mean or geometric mean (as appropriate) PK parameters for (S)-zopiclone dosed as the single enantiomer or as the racemate were compared by an ANOVA and determination of 95% confidence intervals.

The following pharmacokinetic parameters were estimated for each analyte:

- The peak concentration (C_{max}) and time to peak concentration (t_{max})
- The elimination rate constant λ_z ,
- The terminal half-life ($t_{1/2}$)
- The area under the concentration-time curve to the last measurable time point (AUC_{last})

Additionally, the area under the plasma concentration-time curve from zero to infinity (AUC_{inf}).

- Dose proportionality between all doses of (S)-zopiclone was assessed for each analyte using a power model. C_{max} , AUC_{last} , and AUC_{inf} for each analyte was tested for dose proportionality using the following model: $\log(\text{parameter}) = a + b * \log(\text{dose}) + \text{error}$ where a is the intercept and b is the slope. Dose proportionality was assessed based on whether the 95% confidence interval constructed for the estimate of b included the value of 1.0.

RESULTS

Table 12A: Maximum Concentration (C_{max}) For S Zopiclone after S zopiclone administration and R and S Zopiclone following administration of the racemic product

		(S)-Zopiclone Dose						(RS)-Zopiclone Dose			
Dose Group		1.0	2.0	2.5	3.0	3.75	5.0	7.5	2.5	5.0	7.5
(S)-zopiclone	N	6	6	6	6	6	6	10	6	6	6
(ng/mL)	Mean	8.52	17.13	27.07	24.60	24.78	35.82	53.25	11.42	20.83	36.47
	SD	2.00	3.01	9.61	2.74	8.23	8.43	10.01	2.95	5.67	7.67
(R)-zopiclone	N								6	6	6
(ng/mL)	Mean	NA	NA	NA	NA	NA	NA	NA	8.13	12.36	25.42
	SD	NA	NA	NA	NA	NA	NA	NA	3.26	3.41	8.38

Table 13A : AUCinf For S Zopiclone after oral administration of S zopiclone and R and S Zopiclone following the oral administration of the racemic product

Dose Group		(S)-Zopiclone Dose							(RS)-Zopiclone		
		1.0	2.0	2.5	3.0	3.75	5.0	7.5	Dose (mg)		
(S)-zopiclone	N	6	6	6	6	6	6	10	6	6	6
(ng*hr/mL)	Mean	52.1	118.7	174.4	193.3	232.5	360.4	473.9	77.2	160.0	267.5
	SD	11.9	18.6	20.6	54.0	68.1	130.9	157.2	13.3	32.8	50.5
(R)-zopiclone	N								4	6	6
(ng*hr/mL)	Mean	NA	NA	NA	NA	NA	NA	NA	31.9	62.2	111.2
	SD	NA	NA	NA	NA	NA	NA	NA	7.5	17.7	22.6

Table 14A: Half-life (t½) For S Zopiclone after oral administration of S zopiclone and R and S Zopiclone following the oral administration of the racemic product

Dose Group		(S)-Zopiclone Dose							(RS)-Zopiclone Dose		
		1.0	2.0	2.5	3.0	3.75	5.0	7.5	Dose (mg)		
(S)-zopiclone	N	6	6	6	6	6	6	10	6	6	6
(hr)	Mean	4.48	5.53	6.23	5.79	7.42	7.86	6.33	4.93	5.57	5.76
	SD	1.03	1.64	2.04	1.75	1.57	1.89	0.90	0.70	1.36	1.40
(R)-zopiclone	N								4	6	6
(hr)	Mean	NA	NA	NA	NA	NA	NA	NA	2.57	2.99	3.03
	SD	NA	NA	NA	NA	NA	NA	NA	0.61	1.02	0.50

Table 15A : Dose Proportionality of (S)-Zopiclone Cmax Following Oral Administration of (S)-Zopiclone and (RS)-Zopiclone

	(S)-Zopiclone	(RS)-Zopiclone
Slope Estimate	0.860	1.044
Slope Std Error	0.060	0.138
95% CI	0.740-0.980	0.752-1.337

Table 16A: Dose Proportionality of (S)-Zopiclone AUClast Following Oral Administration of (S)-Zopiclone and (RS)-Zopiclone

	(S)-Zopiclone	(RS)-Zopiclone
Slope Estimate	1.133	1.214
Slope Std Error	0.067	0.112
95% CI	0.998-1.268	0.978-1.451

Table 17A: Dose Proportionality of (S)-Zopiclone AUCinf Following Oral Administration of (S)-Zopiclone at doses between 1.0 and 7.5 mg and (RS)-Zopiclone at doses between 2.5 and 7.5 mg.

	(S)-Zopiclone	(RS)-Zopiclone
Slope Estimate	1.071	1.119
Slope Std Error	0.065	0.103
95% CI	0.941-1.202	0.901-1.337

Was there any evidence of in vivo interconversion between S and R Zopiclone.

Table 18A: Summary of mean (S)- zopiclone ratios following oral administration for the 7.5 mg and 5.0 mg dose racemic tablets compared to the 3.75 mg and 2.5 mg S zopiclone tablets respectively.

Parameter	7.5mg tablet RS Zopiclone /3.75 mg tablet S Zopiclone	5.0mg tablet RS Zopiclone /2.5 mg tablet S Zopiclone
Cmax	1.47	0.76
AUCinf	1.15	0.91

Table 19A: Summary of mean S/R zopiclone ratios following oral administration for the 2.5 mg, 5.0 mg and 7.5 mg dose racemic tablets for Cmax

Dose RS	S-zopiclone ng/ml-Cmax	R-zopiclone ng/ml-Cmax	RatioS/R
2.5 mg	11.42	8.13	1.4
5.0 mg	20.83	12.36	1.68
7.5 mg	36.47	25.42	1.43

Table 20A: Summary of mean S/R zopiclone ratios following oral administration for the 2.5 mg, 5.0 mg and 7.5 mg dose racemic tablets for AUCt

Dose RS	S-zopiclone ng/mlxhr AUCt	R-zopiclone ng/mlxhr AUCt	RatioS/R
2.5 mg	67.1	25.7	2.6
5.0 mg	149.2	55.8	2.6
7.5 mg	255.8	104.5	2.4

Table 21A: Half-life ($t_{1/2}$) For S Zopiclone after oral administration of S zopiclone and R and S Zopiclone following the single dose oral administration of the racemic product in healthy normals

Dose Group		(S)-Zopiclone Dose							(RS)-Zopiclone Dose		
		1.0	2.0	2.5	3.0	3.75	5.0	7.5	2.5	5.0	7.5
(S)-zopiclone	N	6	6	6	6	6	6	10	6	6	6
(hr)	Mean	4.48	5.53	6.23	5.79	7.42	7.86	6.33	4.93	5.57	5.76
	SD	1.03	1.64	2.04	1.75	1.57	1.89	0.90	0.70	1.36	1.40

Comments:

1. S-zopiclone does not show any in vivo interconversion to R zopiclone based upon the AUC results. Coefficients of variation of 21-35% result in overlapping values.
2. The pharmacokinetics of single doses of (S)-zopiclone between 1 to 7.5 mg is linear.
3. Half-life of (S)-zopiclone is 4-8 hrs in healthy volunteers for doses up to 7.5 mg.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

6.3.5 Individual Study Report- Protocol 190-002

A DAYTIME, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP, MULTIPLE DAILY DOSE SAFETY AND PHARMACOKINETIC STUDY OF (S)-ZOPICLONE IN HEALTHY VOLUNTEERS

STUDY INTRODUCTION

A single dose-rising study in humans has been completed (Study 190-001), in which single doses up to 7.5 mg (S)-zopiclone were safe and well tolerated when administered to normal, healthy subjects. The more common adverse events (AE) were predominantly related to the expected pharmacological activity of zopiclone (i.e. sleepiness/drowsiness) or were a known side effect of racemic zopiclone (i.e. unpleasant taste). These and other AEs were more prominent at the higher doses of (S)-zopiclone. For this reason, three lower doses (1, 3, and 6 mg) of (S)-zopiclone were chosen for the current study in which the pharmacokinetics of multiple dosing, and food effect, were determined.

STUDY OBJECTIVES To determine the safety, tolerability and PK profile of seven daily doses of (S)-zopiclone (1, 3, 6 mg) compared to placebo in healthy adult volunteers.

To determine the effect, if any, of a high fat meal on the pharmacokinetics of single doses of (S)-zopiclone in healthy adult volunteers.

Secondary Objectives

To determine the effect on daytime sleepiness and psychomotor performance of seven daily daytime doses of (S)-zopiclone compared to placebo in healthy adult volunteers.

Study Design

An oral solution was used in this study. This was a two-center, daytime administration, randomized, double blind, placebo-controlled, parallel-group, in-patient study in healthy male and female volunteers. There were two study periods. During Period 1, subjects were randomized to receive either placebo or one of three dose levels of (S)-zopiclone following a high fat breakfast. PK samples were collected and subjects were discharged following their 48-hour PK blood sample and safety assessments. On Day 7 of Period 1, subjects returned for Period 2, Day -1 assessments. On Day 1 of Period 2, subjects were dosed with the same dose as in Period 1 in the fasted state and PK blood samples were collected for 24 hours. Subjects were dosed on each of Days 2-7 with the same dose as in Period 1 and as on Day 1 of Period 2. On Day 7, prior to and following the dose, PK blood samples were collected through 48 hours post-dosing. Subjects were discharged from the study on Day 9 after review of safety assessment data.

Table 22A: Subject Demographics and Baseline Characteristics

Parameter	Statistic	Period 1*				Period 2*			
		1 mg (N=12)	3 mg (N=12)	6 mg (N=12)	Placebo (N=12)	1 mg (N=11)	3 mg (N=12)	6 mg (N=12)	Placebo (N=11)
Age (yrs)	Mean	30.8	30.6	27.8	28.7	31.8	30.6	27.8	29.5
	SD	8.2	9.3	9.1	6.6	7.7	9.3	9.1	6.3
Gender									
Male	N (%)	8 (66.7)	9 (75.0)	9 (75.0)	9 (75.0)	7 (63.6)	9 (75.0)	9 (75.0)	9 (81.8)
Female	N (%)	4 (33.3)	3 (25.0)	3 (25.0)	3 (25.0)	4 (36.4)	3 (25.0)	3 (25.0)	2 (18.2)
Race									
Caucasian	N (%)	9 (75.0)	10 (83.3)	10 (83.3)	11 (91.7)	8 (72.7)	10 (83.3)	10 (83.3)	10 (90.9)
Black	N (%)	1 (8.3)	2 (16.7)	2 (16.7)	1 (8.3)	1 (9.1)	2 (16.7)	2 (16.7)	1 (9.1)
Hispanic	N (%)	1 (8.3)	0	0	0	1 (9.1)	0	0	0
Other	N (%)	1 (8.3)	0	0	0	1 (9.1)	0	0	0

*Single dose administration after a high fat breakfast.
†Multiple dose administration after fasting (QD Days 1-7).

Sample Collection

Plasma samples were drawn from subjects at the following times: Period 1, Day 1 pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48 hours post-Day 1 dosing; Period 2, Day 1 pre-dose, and at 0.5, 1, 1.5, 2, 3, 5, 6, 8, 14, and 16 hours post-dosing; Period 2 Day 7 pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48 hours post-Day 7 dosing.

Bioanalytical Methods-

Studied Period (years): Clinical Conduct November 15, 1999 to January 15, 2000

Analysis of plasma samples was conducted from

Theoretical Storage time: —

Parameter	S(+)-Zopiclone
Method	LC/MS/MS
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Statistical Analysis

The following PK parameters were estimated for each analyte in each treatment:

- The peak concentration (C_{max}) and time to peak concentration (T_{max}) for all analytes (Period 1, Day 1 and Period 2, Days 1 and 7).
- The terminal rate, λ_z , was estimated for each analyte
- Trough (S)-zopiclone, concentrations (C_T) were determined immediately before dosing on Days 2 through 8 of Period 2 and tested for attainment of steady-state. The measured accumulation ratios, $RAUC$ and RC_{max} , on Day 7 were calculated as:

$$Rauc = AUC(0-24)_{day7} / AUC(0-24)_{day1} \quad \text{and} \quad RC_{max} = C_{max} day7 / C_{max} day1$$

If $AUC(0-24)$ was not able to be calculated on either Day 1 or Day 7, then $RAUC$ was not estimated. (S)-Zopiclone trough concentrations on Days 2 through 8 of Period 2 were tested within each dosage group (using a repeated measures ANOVA model with subject and day effects) to determine whether steady-state was attained by Day 7. The most conservative approach using the last three days (Days 6, 7, and 8) of the interval was tested first for attainment of steady-state. If steady-state was deemed to have been achieved (p-value for day effect >0.05), the previous day was added (e.g. Days 5, 6, 7 and 8) and the statistical analysis rerun. This was done sequentially until a statistically significant difference was found. Steady-state was to be defined as having been achieved on the last day where statistically significant differences were not obtained.

- Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration was calculated using the linear trapezoidal method, namely:

The area under the concentration-time curve to 24 hours (AUC_{0-24}), the area under the concentration-time curve to the last quantifiable concentration (AUC_{last}), and the area under the concentration-time curve to infinity (AUC_{inf}) was calculated for each analyte.

AUC_{0-24} , AUC_{last} and AUC_{inf} were calculated for the fed single dose, fasted single dose, and fasted multiple dose treatments. AUC_{0-24} (representing the dosing interval) was the parameter that was used for the multiple dose treatment comparisons; AUC_{0-24} , AUC_{last} , and AUC_{inf} were reported for the single dose treatments.

- For the multiple dose profiles, dose proportionality between 1.0, 3.0, and 6.0 mg of (S)-zopiclone was assessed for each analyte using a power model. C_{max} and AUC_{0-24} for each analyte were tested for proportionality using the following model:

$$\log(\text{parameter}) = a + b * \log(\text{dose}) + \text{error}$$

where a is the intercept and b is the slope.

Linearity was assessed based on whether 95% confidence intervals constructed for the estimate of b included a value of 1.0

RESULTS

Table 23A: Descriptive Statistics of Cmax and Tmax values for (S)-zopiclone

Parameter	Statistic	Single Dose			Single Dose			Multiple Dose		
		Period 1, Day 1 (Fed)			Period 2, Day 1 (Fasted)			Period 2, Day 7 (Fasted)		
		1 mg	3 mg	6 mg	1 mg	3 mg	6 mg	1 mg	3 mg	6 mg
Cmax (ng/mL)	n	12	12	12	11	12	12	11	12	12
	Mean	6.15	19.88	40.28	10.29	25.48	54.68	9.58	26.18	59.63
	SD	1.12	4.14	10.83	2.69	7.08	19.14	1.79	6.56	19.23
Tmax (hr)	n	12	12	12	11	12	12	11	12	12
	Median	3.0	2.0	3.0	1.0	1.0	1.5	0.5	1.0	1.0
	Range									

Table 24A: Descriptive Statistics of AUC (0-24) and AUC(0-inf) for (S)-zopiclone

Analyte	Parameter	Statistic	Single Dose			Single Dose			Multiple Dose		
			Period 1 (Fed)			Period 2, Day 1 (Fasted)			Period 2, Day 7 (Fasted)		
			1 mg	3 mg	6 mg	1 mg	3 mg	6 mg	1 mg	3 mg	6 mg
(S)-Zopiclone	AUC _(0-∞) (ng*hr/mL)	n	10	12	12	11	12	12	NA	NA	NA
		Mean	58.24	183.02	368.27	62.85	195.74	406.67			
		SD	14.08	50.57	98.14	15.71	64.37	120.81			
	AUC ₍₀₋₂₄₎ (ng*hr/mL)	n	5	12	12	6	11	12	7	12	12
		Mean	54.76	166.21	338.26	62.96	187.76	379.04	66.05	191.07	409.31
		SD	8.06	49.03	90.10	8.42	49.75	110.25	7.90	60.88	116.85

Table 25A: Slope Estimates and 95% Confidence Intervals from the Assessment of Dose proportionality using the power model

Analyte	Parameter	Estimate	Slope Estimates and Confidence Intervals					
			Day 1			Day 7		
			Estimate	Lower	Upper	Estimate	Lower	Upper
(S)-Zopiclone	C _{max}	0.91	0.78	1.05	1.00	0.87	1.12	
	AUC ₍₀₋₂₄₎	0.98	0.84	1.13	1.00	0.85	1.15	

! Slope estimate (b) from power model, log (parameter) = a + b * log(dose) + error.

Table 26A: Geometric Least Squares Mean Ratios and 90% Confidence Intervals for the fed and fasted studies.

Analyte	Parameter	1 mg (S)-Zopiclone			3 mg (S)-Zopiclone			6 mg (S)-Zopiclone		
		Ratio ¹	90% CI (%)		Ratio ¹	90% CI (%)		Ratio ¹	90% CI (%)	
		(%)	Lower	Upper	(%)	Lower	Upper	(%)	Lower	Upper
(S)-zopiclone	C _{max}	60.6	52.4	70.1	78.6	67.7	91.3	74.9	63.5	88.4
	AUC(0-24)	NC	NC	NC	91.5	82.4	101.8	89.3	82.5	96.6
	AUC(0-inf)	90.6	79.8	102.9	95.5	87.1	104.8	90.7	84.1	97.8
	t _{1/2}	114.1	96.4	135.0	108.9	94.4	125.5	106.4	96.5	117.3
¹ Geometric least squares mean ratio (fed/fast)										
NC = Not Calculated sufficient data were not available for statistical analysis.										

Table 27A: Accumulation Ratios for (S)-Zopiclone

Analyte	Parameter	Statistic	Multiple Dose		
			1 mg	3 mg	6 mg
(S)-Zopiclone	RAUC (ng*hr/mL)	N	6	11	12
		Mean	1.06	1.07	1.09
		SD	0.18	0.18	0.13
	RC _{max} (ng*hr/mL)	N	11	12	12
		Mean	0.97	1.04	1.15
		SD	0.24	0.17	0.37

NA = Not Applicable. NC = the summary statistics were not computed for n<3.

RAUC: Accumulation ratio for AUC(0-24) calculated as [AUC(0-24) Period 2, Day 7] / [AUC(0-24) Period 2, Day 1].

RC_{max}: Accumulation ratio for RC_{max} calculated as [RC_{max} Period 2, Day 7] / [RC_{max} Period 2, Day 1].

Comments:

1. Based upon RAUC and RC_{max} values there is no accumulation for S-zopiclone following multiple dosing
2. (S)-zopiclone pharmacokinetics are dose proportional between 1-6 mg following multiple dosing.
3. C_{max} levels for the 3 mg dose are lowered 22% by food whereas extent of absorption is unchanged.

6.3.6 Individual Study Report-Study 190-005 - A DAYTIME, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, RISING DOSE, MULTIPLE DAILY DOSE SAFETY AND PHARMACOKINETIC STUDY OF (S)-ZOPICLONE IN HEALTHY ELDERLY SUBJECTS

Study Introduction and Objectives

The present study assessed the safety and tolerability of a once daily dose of (S)-zopiclone for seven days of daytime administration of 1.0, 2.0, 3.0, and 5.0 mg of (S)-zopiclone compared to placebo and to determine the pharmacokinetic profile in healthy elderly subjects.

OBJECTIVES

The primary objective was to determine the safety and tolerability of a once daily dose of (S)-zopiclone for seven days compared to placebo and to determine the pharmacokinetic profile in healthy elderly subjects administered during the daytime.

A secondary objective was to determine the effect on daytime sleepiness and psychomotor performance of a once daily dose of (S)-zopiclone for seven days of (S)-zopiclone compared to placebo in healthy elderly subjects.

Study Design

This was a two-center, daytime administration, randomized, double-blind, placebo-controlled, rising, multiple dose in-patient study in 36 healthy male and female elderly subjects ages 65 to 79 years old. Doses evaluated were 1.0, 2.0, 3.0, and 5.0 mg of (S)-zopiclone. Dose escalation in (S)-zopiclone was accomplished by evaluating sequential panels of nine subjects each, six of whom were randomized to receive active drug and three to receive placebo. No subject was repeated in a subsequent panel. In each dosage group, subjects received one daily dose for seven days. A panel was not dosed until the safety results from the preceding lower group had been reviewed and it was agreed by the Investigators, the Project Medical Officer (PMO), and the Medical Monitor that it was safe to proceed to the next higher group.

Study medication was administered as a solution of (S)-zopiclone in sodium phosphate buffer, pH 2.7-2.8.

Sample Collection and Handling

Blood samples (5 mL) were collected in lithium heparin coated tubes at the following times:

- Days 1 and 7, prior to dosing and at 30, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, and 16 hours post-dosing;
- Days 2-6, prior to dosing;
- Day 8, 24, 30, and 36 hours following the last dose (Day 7);
- Day 9, 48 hours following the last dose (Day 7).

Samples were kept on ice until centrifuged.

Table 28A: Demographic and Baseline Characteristics

Characteristic	Treatment Group				
	Placebo (N=12)	(S)-Zopiclone 1 mg (N=6)	(S)-Zopiclone 2 mg (N=6)	(S)-Zopiclone 3 mg (N=6)	(S)-Zopiclone 5 mg (N=6)
Gender N	6 (50%)				
Female (%)		2 (33.3%)	0 (0%)	5 (83.3%)	4 (66.7%)
Male (%)	6 (50%)	4 (66.7%)	6 (100%)	1 (16.7%)	2 (33.3%)
Race N					
Caucasian (%)	12 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)
Age (yrs) Mean (\pm SD)	70.2 (3.6)	69.2 (3.5)	68.5 (3.4)	73.8 (4.7)	72.2 (4.4)
Min, Max	65, 77	65, 75	65, 73	67, 79	68, 78

Bioanalytical Methods-

Studied Period (years): Studied Period (years): Clinical Conduct March 7, 2000 to May 18, 2000

Analysis of plasma samples was completed September 2000

Theoretical Storage time: —

Parameter	S(+)-Zopiclone
Method	LC/MS/MS
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	

Statistical Analysis

Individual (S)-zopiclone, plasma concentrations were determined by validated methods at a contract analytical laboratory. (S)-zopiclone urine concentrations were also determined. The

following pharmacokinetic parameters were determined for each treatment and analyte by non-compartmental methods using WinNonlin[®] Professional based on the individual plasma concentration-time data collected after single dose and at steady-state after multiple dose administration.

C_{max} Maximum plasma concentration obtained from inspection of individual concentration-time profiles.

t_{max} Time of occurrence of C_{max} .

C_{last} The last post-dose quantifiable concentration.

T_{last} The time of the last post-dose quantifiable concentration.

λ_z Elimination rate constant obtained from a linear regression of the natural log_e transformed concentration versus time data in the terminal phase.

AUC(0-16) Area under the plasma concentration-time curve from time 0 to 16 hrs, calculated using the linear trapezoidal rule, based on actual sampling times. No interpolation or extrapolation was used in calculating AUC(0-16).

τ Nominal dosing interval.

AUC(0- τ) Area under the plasma concentration-time curve over the dosing interval (τ), calculated using the linear trapezoidal rule, based on actual sample times. No interpolation or extrapolation was used in calculating AUC(0- τ). If the last plasma concentration for the dosing interval was BLQ, then AUC(0- τ) was calculated up to the time of the last quantifiable concentration during the dosing interval; if, however, the time of this last concentration was less than 16 hours, then AUC(0- τ) was considered missing.

AUC(0-inf) Area under the total plasma concentration-time curve for the 0-infinity interval, was calculated by summing the area under the curve from time zero to the time of the last quantifiable concentration (t_{last}) and the extrapolated AUC from t_{last} .

$A_e(0-24)$ The cumulative amount of the analyte excreted in the urine during the time interval 0 to 24 hours.

Renal clearance for an analyte was estimated as the ratio: $Cl_r = A_e(0-24) / AUC(0-\tau)$

$R_{C_{max}}$ Ratio of C_{max} on the last and first days of a multiple dosing regimen, $R_{C_{max}} = C_{max}(7) / C_{max}(1)$, where 1 and 7 refer to the first and last days of drug administration, respectively.

$RAUC$ $RAUC = AUC(0-\tau)(7) / AUC(0-\tau)(1)$, where 1 and 7 refer to the first and last days of drug administration, respectively.

RESULTS

Table 29A: Mean \pm SD (S)-Zopiclone plasma concentrations following Oral dosing of (S)-Zopiclone solution.

Treatment	Time	(S)-Zopiclone Dose			
		1.0 mg	2.0 mg	3.0 mg	5.0 mg
Post-Dose					
Day	(hr)	N=6	N=6	N=6	N=6
Day 1	0	BLQ	BLQ	BLQ	BLQ
	0.5	9.18 \pm 1.41	10.72 \pm 5.54	25.65 \pm 11.80	36.77 \pm 18.60
	1	9.83 \pm 2.38	13.79 \pm 4.86	24.63 \pm 4.99	39.72 \pm 10.39
	1.5	7.47 \pm 1.68	14.27 \pm 2.77	25.20 \pm 4.08	36.42 \pm 10.59
	2	7.49 \pm 2.19	12.07 \pm 1.87	23.55 \pm 3.46	35.93 \pm 10.58
	3	6.18 \pm 1.35	11.12 \pm 0.94	21.27 \pm 5.10	35.37 \pm 12.04
	4	5.25 \pm 1.41	9.62 \pm 1.71	17.88 \pm 4.85	26.70 \pm 6.31
	6	4.02 \pm 1.35	6.73 \pm 1.07	13.42 \pm 2.34	21.03 \pm 6.85
	8	3.45 \pm 0.96	6.23 \pm 0.99	10.92 \pm 3.24	15.45 \pm 6.09
	12	1.90 \pm 0.71	3.89 \pm 0.92	8.63 \pm 2.89	10.18 \pm 5.47
	16	1.09 \pm 0.89	3.07 \pm 0.56	5.32 \pm 2.98	6.60 \pm 3.77
	24	BLQ	1.69 \pm 0.47	3.61 \pm 1.87	3.52 \pm 2.47
Day 7	0	BLQ	2.95 \pm 1.16	5.09 \pm 3.57	5.75 \pm 3.53
	0.5	9.48 \pm 1.40	11.05 \pm 5.03	28.73 \pm 7.79	41.48 \pm 15.33
	1	11.26 \pm 4.01	17.10 \pm 3.86	36.22 \pm 5.65	46.83 \pm 12.64
	1.5	9.41 \pm 3.46	18.03 \pm 3.59	33.83 \pm 7.30	44.37 \pm 13.44
	2	8.75 \pm 2.80	17.07 \pm 2.43	30.08 \pm 9.59	45.23 \pm 13.51
	3	7.50 \pm 2.43	15.43 \pm 2.07	27.17 \pm 9.77	32.33 \pm 12.14
	4	6.46 \pm 1.56	14.08 \pm 2.23	28.80 \pm 9.54	35.28 \pm 10.69
	6	5.18 \pm 1.58	11.78 \pm 1.90	21.22 \pm 9.09	25.33 \pm 7.88
	8	4.61 \pm 1.56	9.35 \pm 1.30	18.54 \pm 8.37	22.20 \pm 7.41
	12	2.84 \pm 1.06	6.34 \pm 0.90	12.93 \pm 8.00	13.94 \pm 5.82
	16	1.76 \pm 0.98	5.01 \pm 1.35	8.46 \pm 5.33	10.68 \pm 5.62
	24	1.04 \pm 0.82	3.00 \pm 1.15	6.17 \pm 4.86	5.82 \pm 3.57
	30	BLQ	1.91 \pm 0.98	3.70 \pm 3.75	2.96 \pm 2.30
	36	BLQ	BLQ	2.44 \pm 3.12	1.53 \pm 1.52
	48	BLQ	BLQ	BLQ	BLQ

BLQ = Below the limit of quantitation

Table 30A: Mean \pm SD (S)-Zopiclone Urine Amounts (μ g) Following Oral Dosing of (S)-Zopiclone

Treatment	Time	(S)-Zopiclone Dose			
		1.0 mg	2.0 mg	3.0 mg	5.0 mg
Day	Interval	N=6	N=6	N=6	N=6

Day 1	0 6 hr	40 ± 32	51 ± 23	83 ± 53	130 ± 70
	6 24 hr	30 ± 25	83 ± 33	125 ± 61	169 ± 75
Day 7	0 6 hr	35 ± 19	63 ± 33	74 ± 34	113 ± 41
	6 24 hr	44 ± 21	151 ± 38	155 ± 38	163 ± 76

Table 31A: Summary Statistics of (S)-Zopiclone Pharmacokinetic Parameters Following Oral Dose of (S)-Zopiclone solution.

Parameter		Day 1				Day 7			
		1.0 mg	2.0 mg	3.0 mg	5.0 mg	1.0 mg	2.0 mg	3.0 mg	5.0 mg
Cmax (ng/mL)	N	6	6	6	6	6	6	6	6
	Mean	10.58	15.32	29.50	46.98	11.97	18.67	37.60	50.28
	SD	1.76	3.37	8.20	11.52	3.49	2.98	6.11	12.47
Tmax (hr)	N	6	6	6	6	6	6	6	6
	Median	0.75	1.25	1.00	1.00	0.75	1.50	1.00	1.00
	Range								
AUC (0-∞) (ng*hr/mL)	N	4	6	6	6	5	6	6	6
	Mean	75.90	126.67	243.74	337.93	95.77	192.17	368.79	447.31
	SD	12.79	18.04	67.15	122.37	27.89	29.94	161.13	142.50
AUC (0-inf) (ng*hr/mL)	N	6	6	6	6	6	6	6	6
	Mean	75.90	149.31	296.02	374.86	104.99	236.04	463.06	511.44
	SD	24.19	22.86	103.72	156.15	35.51	58.42	262.22	188.64
t1/2 (hr)	N	6	6	6	6	6	6	6	6
	Mean	6.40	8.97	9.05	6.56	7.83	9.85	9.55	7.52
	SD	2.02	1.86	2.39	1.30	1.57	2.48	2.82	1.67
Clr (L/hr)	N	4	6	6	6	5	6	6	6
	Mean	1.26	1.06	0.85	0.91	0.92	1.10	0.67	0.61
	SD	0.82	0.24	0.34	0.40	0.15	0.17	0.19	0.07
Recovery (%)	N	6	6	6	6	6	6	6	6
	Mean	6.95	6.71	6.93	5.98	7.97	10.68	7.65	5.52
	SD	5.59	1.62	3.25	2.76	3.17	2.90	1.89	2.08

Table 32A: Dose Proportionality of (S)-Zopiclone C_{max} and AUC(0-t) Following Oral Administration of (S)-Zopiclone in the elderly

	C _{max}		AUC(0-t)	
	Day 1	Day 7	Day 1	Day 7
Slope Estimate	0.95	0.94	0.95	0.99
Slope Std Error	0.09	0.08	0.09	0.12
95% CI	0.77, 1.13	0.77, 1.12	0.76, 1.15	0.74, 1.24

Table 33A: Accumulation Ratios for (S)-Zopiclone for elderly based upon mean data(Day7/Day1)

Analyte	Parameter	Statistic	Multiple Dose Period 2, Day 7 (Fasted)			
			1 mg	2 mg	3 mg	5 mg
(S)-Zopiclone	RAUC(0-inf) (ng*hr/mL)	Mean	1.38	1.58	1.56	1.36
	RC _{max} (ng*hr/mL)	Mean	1.13	1.21	1.27	1.07

Comments:

1. The pharmacokinetics of esopiclone in the elderly appear to be linear based upon the log model.
2. The half-life varies between 6-10 hrs in the elderly, which appears to be longer than that observed in healthy normals 4-8 hrs.
3. 6-10% of the drug is excreted in the urine unchanged.
4. There is drug accumulation in the elderly population since the theoretical value based upon $(1/1-e^{-k_{tau}})$ was calculated to range from 1.08-1.22 dependent upon half-life (6hr-10 hrs).

**6.3.7 Individual Study Report- PROTOCOL NO: 190-013
 PHARMACOKINETICS OF ORALLY ADMINISTERED ESOPICLONE IN SUBJECTS
 WITH MILD-TO-MODERATE AND MODERATE-TO-SEVERE HEPATIC
 DYSFUNCTION**

Study Introduction and Objectives

To describe and compare the pharmacokinetics of esopiclone and its metabolite in subjects with impaired hepatic function and gender-, age-, and weight-matched normal subjects.

To describe and compare the safety and tolerability of a single dose of esopiclone in subjects with impaired hepatic function and gender-, age-, and weight-matched normal subjects.

Study Design

This was a multicenter open-label study. A total of 24 subjects with hepatic impairment (8 subjects each with mild-to-moderate, moderate-to-severe, and severe impairment) and 16 healthy subjects were enrolled and completed. The study consisted of a screening visit (Visit 1) and a treatment visit (Visit 2). At Visit 1, subjects were evaluated for eligibility, and their degree of hepatic impairment was assessed based on the Child-Pugh classification system. Eligible subjects received a single oral dose of esopiclone 2 mg at Visit 2. Subjects were sequentially dosed, beginning with those who had a Child-Pugh score of 5 or 6, followed by those who had a Child-Pugh score greater than 6, those who had a Child-Pugh score greater than 8, and those with normal hepatic function. Subjects remained in the clinic for approximately 120 hours following dosing. During this time, subjects provided blood and urine samples for pharmacokinetic analysis and underwent safety assessments.

Product Administered: 2 x 1.0 mg tablets of esopiclone

The following Child-Pugh classification was used:

Table 34A: Child-Pugh Classification System of Chronic Liver Disease

Risk Factor	Score		
	1	2	3
Ascites	Absent	Slight	Moderate
Neurologic symptoms	Absent	Transient or mild	Hepatic coma
Prolongation of prothrombin time vs control (s)	<4	4-6	>6
Serum bilirubin (mg/dL)	<2	2-3	>3
Serum bilirubin for subjects with primary	<4	4-10	>10

biliary cirrhosis (mg/dL)			
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
A: Total score=5 to 6 (mild hepatic impairment)			
B: Total score=7 to 9 (moderate hepatic impairment)			
C1: Total score=10 to 12 (severe hepatic impairment)			
C2: Total score>13 (exclude)			

Sample Collection and Handling

Day 1

Serial blood samples were collected for pharmacokinetic analysis at 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 16 hours postdose.

Day 2

Blood samples were collected for pharmacokinetic analysis at 24, 30, and 36 hours postdose.

Days 3-6

Blood samples were collected at the following 48, 72, 96, and 120 hours.

Urine samples for determination of esopiclone were collected at the following postdose intervals: -8-to-0, 0-24, 24-48, 48-72, 72-96, and 96-120 hours.

Table 35A: Baseline Age, Height, Weight, and Child-Pugh Classification by Hepatic Function Group

	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)	Overall p-value
Age (years)					
Mean (SD)	42.1 (12.0)	47.6 (10.5)	57.5 (6.5)	46.6 (3.5)	0.010
Min, max	23, 56	34, 66	49, 68	41, 52	
Height (cm)					
Mean (SD)	173.1 (7.9)	167.0 (10.2)	174.2 (7.6)	169.6 (11.5)	0.318
Min, max	153, 182	158, 188	163, 183	155, 184	
Weight (kg)					
Mean (SD)	78.8 (13.2)	80.3 (10.8)	97.8 (22.2)	73.4 (18.0)	0.183
Min, max	50, 101	58, 92	69, 127	51, 94	
Child-Pugh classification					
Mean (SD)	ND	5.0 (0.0)	8.0 (0.9)	9.9 (0.6)	ND
Min, max	ND	5, 5	7, 9	9, 11	
Note: ND=not determined.					

Bioanalytical Methods-

Studied Period (years): Clinical Conduct October 12, 2000- August 13, 2001

Analysis of plasma samples was conducted from

Theoretical Storage time: —

Parameter	Zopiclone-Plasma	(S)- Zopiclone-Urine
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		

Statistical Analysis

Pharmacokinetic Analysis

For each analyte, individual plasma concentrations at each time blood samples were collected and pharmacokinetic parameters were summarized by hepatic function group using descriptive statistics [number of subjects, mean, median, standard deviation, CV (%), minimum, and maximum]. Individual and mean pharmacokinetic profiles were plotted on linear and logarithmic coordinates. Individual urine amount and concentrations during each collection interval were also summarized by hepatic function group using descriptive statistics. The analysis of the effect of hepatic impairment on the pharmacokinetics of oral esopiclone was conducted using the esopiclone and (S)-desmethylzopiclone pharmacokinetic parameters C_{max} , t_{max} , $AUC_{(0-last)}$, $AUC_{(0-\infty)}$, $AUC_{(t1-t2)}$, Cl_r , $t_{1/2}$, and % recovery of esopiclone in urine.

Visual assessment of the effect of hepatic impairment was performed for each analyte by examining plots of pharmacokinetic parameters versus hepatic impairment group and by plotting selected pharmacokinetic parameters versus Child-Pugh scores. Primary Pharmacokinetic Analysis: The primary analysis was conducted using the esopiclone PK parameters $AUC_{(0-last)}$ and C_{max} . The effect of hepatic impairment was assessed using a one-way analysis of variance (ANOVA/ANCOVA) with hepatic impairment group as the single factor. If age, height, or weight differed significantly across hepatic impairment groups, it was added as a covariate to the model. The pharmacokinetic parameter data were natural log-transformed before analysis. From this ANOVA, least squares means for each group, estimated group differences, and 90%

confidence intervals for group differences were calculated. These results were transformed to the original scale by exponentiation to obtain geometric least square means, ratios of geometric least squares means, and 90% confidence intervals of these ratios. Each of the three hepatic impairment groups was compared to the normal healthy subject group as the reference. If the 90% confidence intervals for comparing each of the three hepatic impairment groups to the normal healthy subject group fell within 80-125% for $AUC_{(0-last)}$ and C_{max} , then it was concluded that hepatic impairment did not affect the pharmacokinetics of esopiclone.

RESULTS

Table 36A: Mean±SD Plasma Concentrations of Esopiclone Following Oral Administration of 2 mg of Esopiclone in Normal Subjects and Subjects with Mild-to-Moderate, Moderate-to-Severe, and Severe Hepatic Impairment

Day	Time (h)	Esopiclone concentration (ng/mL)			
		Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
1	Pre-dose	BLQ	BLQ	BLQ	BLQ
	0.5	17.3 ± 7.8	11.2 ± 8.8	14.5 ± 4.8	13.7 ± 12.6
	1	23.1 ± 7.8	20.5 ± 7.2	17.0 ± 8.6	16.7 ± 10.5
	1.5	20.6 ± 5.2	19.7 ± 6.2	15.6 ± 5.1	17.5 ± 10.8
	2	21.1 ± 5.4	19.2 ± 6.0	15.3 ± 5.1	18.1 ± 9.2
	4	14.8 ± 5.8	12.8 ± 3.7	13.3 ± 6.0	16.8 ± 7.1
	6	10.0 ± 4.1	9.7 ± 2.5	9.4 ± 3.4	14.1 ± 7.0
	8	8.0 ± 3.4	7.8 ± 2.2	8.4 ± 3.4	12.1 ± 6.0
	12	4.7 ± 2.5	4.7 ± 1.5	5.4 ± 2.0	9.5 ± 5.2
	16	2.8 ± 1.4	3.3 ± 1.1	4.3 ± 2.1	7.3 ± 3.8
2	24	1.3 ± 1.5	1.4 ± 1.1	2.7 ± 1.3	5.5 ± 3.7
	30	BLQ	BLQ	2.0 ± 1.4	3.8 ± 2.9
	36	BLQ	BLQ	BLQ ^a	2.5 ± 2.0
3	48	BLQ	BLQ	BLQ ^a	1.5 ± 1.5
4	72	BLQ	BLQ	BLQ ^a	BLQ
5	96	BLQ	BLQ	BLQ ^a	BLQ
6	120	BLQ	BLQ	BLQ ^a	BLQ

Notes: Mean (±SD) values were calculated when at least 3 subjects had measurable concentrations for a given timepoint.
 BLQ=below limit of quantification /
 a N=7

Table 37A: Mean±SD Esopiclone Urine Amounts (µg) Following Oral Administration of 2 mg of Esopiclone in Normal Subjects and Subjects with Mild-to-Moderate, Moderate-to-Severe, and Severe Hepatic Impairment

Time Interval(h)	Hepatic Function Group			
	Normal (N=16)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Pre-dose	BLQ ^a	BLQ ^a	BLQ	BLQ
0-24	108.9 ± 29.4	144.6 ± 72.8	104.8 ± 62.5	89.0 ± 41.5
24-48	5.0 ± 12.7	4.0 ± 11.3	10.7 ± 16.4	34.8 ± 34.0

48 72	BLQ	BLQ	BLQ ^c	11.7 ± 27.6
72 96	BLQ ^b	BLQ ^d	BLQ ^e	3.6 ± 10.0
96 120	BLQ	BLQ	BLQ ^e	BLQ ^e
Note: BLQ=below limit of quantification.				
a N=13				
b N=14				
c N=4				
d N=6				
e N=7				

Table 38A: Mean±SD Pharmacokinetic Parameters of Esopiclone Following Oral Administration of 2 mg of Esopiclone in Normal Subjects and Subjects with Mild-to-Moderate, Moderate-to-Severe, and Severe Hepatic Impairment

Parameter	Normal (N=16)	Hepatic Function Group		
		Mild (N=8)	Moderate (N=8)	Severe (N=8)
C _{max} (ng/mL)	25.1 ± 8.0	23.0 ± 7.0	20.6 ± 6.7	20.5 ± 9.3
AUC(0-last) (ng h/mL)	172.2 ± 72.2	165.0 ± 50.1	195.2 ± 75.6	325.6 ± 204.8
AUC(0-∞) (ng h/mL)	188.1 ± 75.0	179.3 ± 50.5	221.4 ± 91.7 ^b	364.2 ± 209.0
t _{1/2} (h)	6.66 ± 2.14	6.79 ± 1.75	11.05 ± 5.64 ^b	15.34 ± 6.06
t _{max} ^a (h)	1.01	1.00	1.00	1.50
Cl _r (L/h)	0.727 ± 0.391 ^c	0.899 ± 0.399	0.682 ± 0.323 ^b	0.460 ± 0.318
Urine recovery (%)	5.69 ± 1.64	7.43 ± 4.01	5.78 ± 3.72	6.96 ± 4.34
a Expressed as median [range].				
b N=7				
c N=15				

Table 39A: Statistical Comparison of Esopiclone Pharmacokinetic Parameters Between Subjects with Hepatic Impairment and Normal Subjects

Parameter	Group	N	Mean	Comparison	Ratio (%)	90% CI
	Moderate	8	17.9	Moderate/Normal	70.79	[53.0, 94.5]
	Severe	8	18.9	Severe/Normal	75.00	[58.4, 96.3]
	Normal	16	25.2			
AUC(0-last) (ng-h/mL)	Mild	8	157.8	Mild/Normal	95.66	[69.6, 131.5]
	Moderate	8	167.1	Moderate/Normal	101.29	[70.3, 145.9]
	Severe	8	287.2	Severe/Normal	174.09	[127.0, 238.7]
	Normal	16	165.0			

Further analysis of the regression of AUC(0-t) was done following elimination of the subject with a severe classification and AUC(0-t) of 797 ng/mlxhr. The resulting regression equations for Child-Pugh Score vs AUC(0-t) were:

	Slope	Intercept	Rsq
AUC(0-t)-All Data	28.09	14.39	0.20
AUC(0-t)> 500 deleted	17.85	74.85	0.25
Cmax	-0.31	23.70	0.008

An additional analysis was done by the reviewer to compare the total sleep time for normals and elderly to determine what AUClast values seemed to be associated with sleep time at the 2 mg dose. A proc univariate analysis was also done to determine the 75th percentile for the data set to see which values were the extremes for each group. The dose vs sleep time plot are presented in Figures 2A and 3A.

Figure 2A: Total sleep time vs dose in normals

Figure 3A: Total sleep time vs dose in elderly

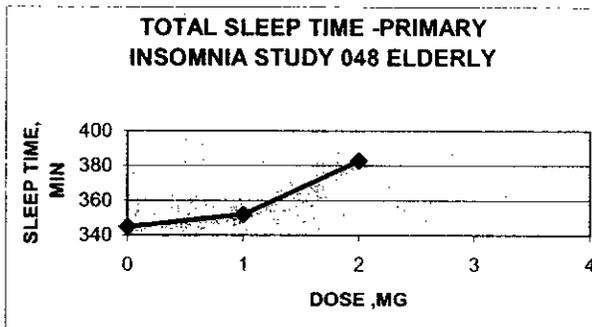
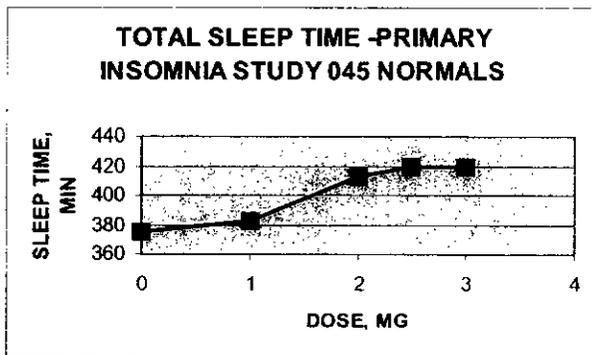


Table 40A. Comparison of the sleep time, extreme AUClast, 75th percentile for AUClast and the firm's recommended dose for each treatment group.

Dose= 2 mg	TOTAL SLEEP TIME	EXTREME AUClast	75 TH PERCENTILE AUClast	RECOMMENDED DOSE
NORMALS	412 MIN	131 NG/ML X HR	123 NG/ML X HR	2-3 MG
ELDERLY	383 MIN	147 NG/ML X HR	139.6 NG/ML X HR	2 MG
SEVERE LIVER DAMAGE	N/A	797.4 NG/ML X HR	234 NG/ML X HR	2 MG

Comments:

1. The storage time for the samples in this study was 13 months (October 2000-November 2001). However the firm's assay validation only covered a period of . . .
2. The firm's plasma assay for study 013 lists Zopiclone as the analyte in plasma however, in urine they list (S)-Zopiclone. This needs to be clarified as to which species is being analyzed in plasma and urine.
3. The pharmacokinetics was comparable between the mild and moderate hepatic dysfunction patients versus normals. However, in the severe disease group the AUC was almost double compared to normals. It seems appropriate to consider a lower than 2 mg dose for individuals with severe liver impairment and that may also be for the elderly. Currently there is no scored tablet or lower strength available other than the 2 mg tablet..

6.3.8 Individual Study Report- PHARMACOKINETICS OF ORALLY ADMINISTERED (S)-ZOPICLONE IN SUBJECTS WITH MILD TO SEVERE RENAL INSUFFICIENCY

STUDY 190-014

Study Introduction and Objectives

The primary objective was to describe and compare the pharmacokinetic profiles of esopiclone and (S)-desmethylzopiclone following a single, 3 mg dose of esopiclone in subjects with renal insufficiency and normal renal function. The secondary objective was to evaluate the safety and tolerability of a single, 3 mg dose of esopiclone in subjects with normal renal function and subjects with renal insufficiency.

Study Design

This was an open-label, single-dose study conducted at multiple inpatient clinical sites enrolling a total of 40 subjects, who were categorized into one of four groups by creatinine clearance (i.e., three groups of 8 subjects with renal impairment (mild, moderate, or severe) and one group of 16 healthy subjects). Subjects were categorized into one of the four groups based on creatinine clearance at the time of screening as outlined in the Guidance for Industry –“Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling” issued by the Food and Drug Administration.

The following Table summarizes the mean baseline creatinine clearance by renal function group.

Group	Creatinine Clearance (mL/min)
1 (normal)	> 80
2 (mild)	>50 < 80
3 (moderate)	>30 <50
4 (severe)	< 30

Table 41A: Demographic and Baseline Characteristics

Characteristic	Statistic	Renal Function Group				p-value ^a
		Normal (N=16)	Mild (N =8)	Moderate (N =8)	Severe (N =8)	
Age	Mean (yr)	43.6	50.1	49.3	51.8	0.3179
	SD (yr)	11.9	9.4	9.8	11.1	
	Min, Max	23, 58	38, 61	32, 64	32, 62	
Gender						
Male	N (%)	9 (56.3%)	6 (75.0%)	6 (75.0%)	5 (62.5%)	
Female	N (%)	7 (43.8%)	2 (25.0%)	2 (25.0%)	3 (37.5%)	
Race						
Caucasian	N (%)	15 (93.8%)	7 (87.5%)	5 (62.5%)	6 (75.0%)	
Black	N (%)	1 (6.3%)	1 (12.5%)	2 (25.0%)	1 (12.5%)	

Asian	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hispanic	N (%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	
Other	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Height	Mean (cm)	170.6	167.5	177.2	170.2	0.1419
	SD (cm)	8.1	6.8	8.1	12.3	
	Min, Max	152, 182	160, 179	163, 185	154, 191	
Weight	Mean (kg)	68.8	71.2	90.4	78.5	0.0473
	SD (kg)	11.4	5.7	22.3	21.0	
	Min, Max	52, 92	63, 78	46, 114	49, 122	
BMI	Mean (kg/mg2)	23.6	25.4	28.5	26.9	
	SD (kg/mg2)	3.0	2.5	5.9	5.5	
	Min, Max	20, 30	23, 29	17, 36	18, 36	
Baseline CLcr	N	16	8	8	7	
	Mean (mL/min)	120.6	66.9	46.0	22.4	
	SD (mL/min)	28.2	12.6	10.9	5.5	
	Min, Max					
a Statistical inference for age, weight, and height was performed using Kruskal-Wallis test.						
Reference: Table 14.1.2.						

Treatment Administered:

Study medication (2 x 1.5 mg tablets) was administered orally on Day 1. The tablets were taken with 240 mL of water.

Sample Collection and Handling

Plasma samples for PK analysis were drawn from subjects at the following times:

Day 1 (Visit 2) pre-dose and at +0.5, +1, +1.5, +2, +4, +6, +8, +12, +16 hours post-dose

Day 2 (Visit 2) at +24, +30, and +36 hours post-dose

Day 3 (Visit 2) at +48 hours post-dose

Day 4 (Visit 2) +72 hours post-dose.

Urine samples for PK analysis were collected from subjects as follows:

A 24-hour urine sample was collected at Screening (Visit 1)

A urine sample was collected within 1 hour prior to dosing at Day 1 (Visit 1)

A 0-6 hour cumulative sample was collected at Day 1 (Visit 2)

A 6-24 hour cumulative sample was collected from Day 1 to Day 2(Visit 2)

A 24-48 hour cumulative sample was collected from Day 2 to Day 3(Visit 2)

A 48-72 hour cumulative sample was collected from Day 3 to Day 4(Visit 2)

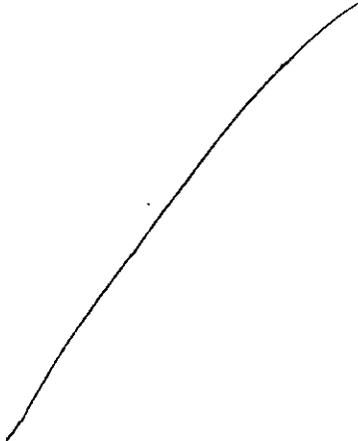
Bioanalytical Methods-

Studied Period (years): Clinical Conduct October 10, 2000- August 2, 2001

Analysis of plasma samples was conducted from —

Theoretical Storage time: —

Parameter	(S)- Zopiclone-Plasma	(S)- Zopiclone-Urine
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples		



Statistical Analysis

The following pharmacokinetic parameters, determined by non-compartmental methods using WinNonlin® Professional, version 3.1 were based on the individual esopiclone and (S)-desmethylopiclone concentration-time data collected after a single oral dose administration.

C_{max}	Maximum observed concentration.
t_{max}	Time of occurrence of C_{max}
C_{last}	The last post-dose quantifiable concentration
t_{last}	The time of the last post-dose quantifiable concentration
λ_z	Elimination rate constant obtained from a linear regression of the natural log (ln) transformed concentration versus time data in the terminal phase.
$t_{1/2}$	Terminal phase half-life,
$AUC(0-last)$	Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration
$AUC(0-\infty)$	Area under the plasma concentration-time curve for the 0-infinity interval,
$AUC(t1-t2)$	Area under the plasma concentration time curve from time t1 to t2, calculated using the linear trapezoidal rule, based on actual sample times.
$A_e(t1-t2)$	The cumulative amount of the analyte excreted during the time interval t1 to t2
Cl _r	Renal clearance for an analyte was estimated as the ratio:

$$Cl_r = A_e(t_{1-2}) / AUC(t_{1-2})$$

Urine Recovery The urine recovery was calculated as $(A_e(0-t_{last}) / \text{Dose}) * 100$.

RESULTS

Table 42A: Mean \pm SD Plasma Concentrations of Esopiclone Following Oral Administration of 3.0 mg Esopiclone in Normal Subjects and Subjects with Mild, Moderate and Severe Renal Impairment

Day	Time (hr)	Esopiclone concentration (ng/mL)			
		Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
1	Pre-dose	BLQ	BLQ	BLQ	BLQ
	0.5	22.3 \pm 19.6	29.4 \pm 17.9	21.1 \pm 15.2	25.4 \pm 16.3
	1	30.5 \pm 11.6	37.8 \pm 11.7	27.9 \pm 10.0	41.5 \pm 15.7
	1.5	29.3 \pm 7.4	36.5 \pm 8.7	28.1 \pm 8.6	34.8 \pm 13.0
	2	28.2 \pm 7.5	33.0 \pm 7.0	26.8 \pm 6.2	35.2 \pm 10.3
	4	22.7 \pm 6.5	26.7 \pm 4.6	23.8 \pm 4.5	27.8 \pm 8.4
	6	17.4 \pm 5.6	22.3 \pm 4.8	18.6 \pm 3.7	22.0 \pm 8.7
	8	13.1 \pm 4.4	16.8 \pm 5.2	13.5 \pm 3.1	16.8 \pm 5.8
	12	7.7 \pm 3.3	10.8 \pm 4.4	8.8 \pm 3.0	11.1 \pm 3.9
	16	4.5 \pm 2.3	6.1 \pm 2.7	6.0 \pm 2.0	6.8 \pm 3.4
2	24	2.1 \pm 1.4	3.9 \pm 1.8	2.9 \pm 1.0	4.0 \pm 2.3
	30	BLQ	2.0 \pm 1.5	1.7 \pm 0.9	2.5 \pm 1.6
	36	BLQ	BLQ	BLQ	1.2 \pm 1.1
3	48	BLQ	BLQ	BLQ	BLQ
4	72	BLQ	BLQ	BLQ	BLQ

BLQ: Below limit of quantification (—).

Table 43A: Mean \pm SD Esopiclone Urine Amounts (μ g) Following Oral Administration of 3.0 mg Esopiclone in Normal Subjects and Subjects with Mild, Moderate and Severe Renal Impairment

Time Interval	Renal Function Group			
	Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
0-6 hr	107.7 \pm 69.4 ^a	90.8 \pm 110.6	77.7 \pm 39.3	64.7 \pm 32.1
6-24 hr	91.4 \pm 52.1	94.8 \pm 87.3	85.1 \pm 68.0	74.7 \pm 30.5
24-48 hr	3.5 \pm 9.7	16.8 \pm 20.3	14.5 \pm 21.4	8.3 \pm 12.0
48-72 hr	NQ	NQ	NQ	NQ

NQ: Not quantifiable.

n = 15				
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Table 44A: Mean ± SD Pharmacokinetic Parameters of Esopiclone Following Oral Administration of 3.0 mg Esopiclone in Normal Subjects and Subjects with Mild, Moderate and Severe Renal Impairment

Parameter	Renal Function Group			
	Normal (n=16)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
C _{max} (ng/mL)	36.7 ± 11.4	43.1 ± 10.6	32.4 ± 7.8	43.4 ± 15.4
AUC _(0-last) (ng hr/mL)	271.0 ± 87.3	372.3 ± 118.2	304.7 ± 77.8	385.6 ± 139.4
AUC _(0-∞) (ng hr/mL)	284.5 ± 91.4	388.3 ± 119.6	319.1 ± 78.5	400.8 ± 141.6
t _{1/2} (hr)	6.12 ± 1.94	7.30 ± 1.09	7.60 ± 1.66	8.16 ± 2.59
t _{max} ^a (hr)	1.25	1.00	1.00	1.00
Cl _r (L/hr)	0.811 ± 0.471 ^b	0.564 ± 0.593	0.614 ± 0.440	0.496 ± 0.396
Recovery (%)	6.76 ± 3.53 ^c	6.75 ± 6.65	5.91 ± 3.81	4.92 ± 2.13
^a expressed as median [range].				
^b n=14				
^c n=15				

Table 45A: Statistical Comparison of Esopiclone Pharmacokinetic Parameters Between Subjects with Renal Impairment and Normal Subjects

Parameter	Group	n	Geometric		
			LS Mean	Comparison	Ratio (%) 90% CI
C _{max} (ng/mL)	Mild	8	40.5	Mild/Normal	122.49 [97.5, 153.8]
	Moderate	8	35.5	Moderate/Normal	88.28 [83.1, 139.2]
	Severe	8	41.4	Severe/Normal	125.24 [99.1, 158.2]
	Normal	16	33.0		
AUC _(0-last) (ng·hr/mL)	Mild	8	349.0	Mild/Normal	141.20 [108.8, 183.2]
	Moderate	8	319.7	Moderate/Normal	129.35 [96.3, 173.7]
	Severe	8	362.2	Severe/Normal	146.54 [112.2, 191.5]
	Normal	16	247.2		
AUC _(0-∞) (ng·hr/mL)	Mild	8	365.2	Mild/Normal	140.22 [108.9, 180.6]
	Moderate	8	334.0	Moderate/Normal	128.25 [96.3, 170.8]

	Severe	8	377.8	Severe/Normal	145.05	[111.9, 188.1]
	Normal	16	260.5			
t_{1/2} (hr)	Mild	8	7.29	Mild/Normal	121.95	[101.4, 146.7]
	Moderate	8	7.23	Moderate/Normal	120.89	[98.1, 149.0]
	Severe	8	7.76	Severe/Normal	129.77	[107.4, 156.9]
	Normal	16	5.98			
Cl_r (L/hr)	Mild	8	0.387	Mild/Normal	46.69	[25.5, 85.6]
	Moderate	8	0.267	Moderate/Normal	32.23	[16.4, 63.4]
	Severe	8	0.374	Severe/Normal	45.22	[24.4, 83.9]
	Normal	14	0.828			

Table 46A: Slope Parameter from the Regression Analysis between Esopiclone Pharmacokinetic Parameters and Baseline Creatinine Clearance

Parameter	Estimate	SE	95% CI	r
C _{max} (ng/mL)	-0.025	0.043	[-0.112, 0.062]	-0.10
AUC(0-last) (ng hr/mL)	-0.851	0.396	[-1.654, -0.047]	-0.33
Cl _r (L/hr)	0.0031	0.0017	[-0.0004, 0.0066]	0.29

Comments:

1. The storage time for the samples in this study was 13 months (October 2000-November 2001). However the firm's assay validation only covered a period of ~

2. There was a 45% increase in AUC between normals and individuals with severe renal impairment. However, since there is only 6% of unchanged (S)-eszopiclone excreted in the urine an adjustment in dose is not required for people with severe renal impairment.

6.4 NONCLINICAL ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION STUDIES OF ESOPICLONE UTILIZING HUMAN BIOMATERIALS

6.4.1 PERMEABILITY

Sepracor Document No. 190-542. Evaluation of permeability classification for (S)-zopiclone using the Caco-2 in vitro model of epithelial monolayers. Study No. CAN-2001-0298-ADM, 2001

The purpose of this study was to determine the permeability of (S)-Zopiclone across human intestinal Caco-2 monolayers.

Method: Caco-2 cells were grown for 7 days to form confluent monolayers with tight cellular junctions and functional brush borders. Caco-2 model absorptive standards were run in the apical to basolateral direction prior to running (S)-Zopiclone experiments to determine the quality of Caco-2 monolayers. The Papp values for the permeability standards mannitol (low permeability) and ketoprofen (high permeability) were $0.63 \pm 0.16 \text{ E-}06 \text{ cm/sec}$ and $70.70 \pm 17.56 \text{ E-}06 \text{ cm/sec}$, respectively. L-Phenylalanine the active transport standard had a Papp values of $20.60 \pm 1.69 \text{ E-}06 \text{ cm/sec}$. All three standards were within the acceptable range for this model. Vinblastine sulfate (high efflux) transport was used to monitor the quality of the secretory efflux mechanisms for these Caco-2 monolayers. Vinblastine sulfate had a secretory efflux ratio of 9.40 compared to the negative efflux standard mannitol with an efflux ratio of 0.40.

Results: An initial portion of this study was to run a mannitol integrity test in the presence of (S)-Zopiclone at the high transport target concentration of $100 \mu\text{M}$. Mannitol transport across the Caco-2 monolayers was determined in the absence and presence of (S)-Zopiclone. Mannitol percent transport was not significantly increased with $100 \mu\text{M}$ (S)-Zopiclone in either transport direction.

Caco-2 permeability of (S)-Zopiclone in the absorptive transport direction was 60.80 ± 10.41 , 59.48 ± 6.51 , and $73.95 \pm 2.70 \text{ E-}06 \text{ cm/sec}$ at 1, 10, and $100 \mu\text{M}$, respectively. These values were greater than the high permeability standard ketoprofen with a Papp value of $44.25 \pm 15.61 \text{ E-}06 \text{ cm/sec}$ indicating that (S)-Zopiclone is a highly transported compound across Caco-2 monolayers.

Secretory efflux of (S)-Zopiclone was similar or less than its absorptive transport. The efflux ratios (BL to AP/AP to BL) were 0.87, 1.02, and 0.71 with 1, 10, and $100 \mu\text{M}$ (S)-Zopiclone. An efflux ratio of 1.0 or less indicates that there is no active efflux mechanism for (S)-Zopiclone at the concentrations tested.

Conclusion: (S)-Zopiclone did not have any effect on the integrity between the Caco-2 cell monolayers at the highest test concentration. (S)-Zopiclone exhibited high absorptive and secretory permeability at all three test concentrations. (S)-Zopiclone did not exhibit any active transport mechanisms in either the absorptive or secretory directions.

6.4.2 Sepracor Study Document No. 190-528. [¹⁴C]-(S)-Zopiclone: in vitro blood-to-plasma partitioning and plasma protein binding in the mouse, rat, dog and human.

Objective:

This study was designed to determine blood-to-plasma partitioning ratios and the percent of binding of [¹⁴C]-(S)-zopiclone to protein in mouse, rat, dog and human plasma using ultrafiltration methods.

Methods:

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2.7.4. BLOOD-TO-PLASMA PARTITION STUDY

Blood samples were spiked with [¹⁴C]-(S)-zopiclone as described in Section 2.8.3 at the appropriate concentrations and incubated at approximately 37°C for approximately 30 minutes.

Three aliquots (10-100 µL) of the spiked blood at each concentration level were placed on _____, air-dried and combusted in a _____. The samples were analyzed for radioactivity as described as in Section 2.8.9.

The remaining spiked blood at each concentration was centrifuged at approximately 37°C for 10 minutes at approximately 3000 rpm. Three aliquots of each harvested plasma sample were analyzed for radioactivity, as described as in Section 2.8.9. Aliquots of blood and plasma taken for radioanalysis were measured using a positive-displacement pipette. The size of all aliquots was recorded.

2.7.5. PROTEIN BINDING STUDY

Plasma samples were spiked with [¹⁴C]-(S)-zopiclone as described in Section 2.8.3 at the appropriate concentrations and incubated at approximately 37°C for approximately 30 minutes.

Three aliquots (10-100 µL) of each incubated spiked plasma sample were analyzed for radioactivity, as described in Section 2.8.9.

Three 1 mL sub-samples of each incubated plasma sample were ultrafiltered, as described in Section 2.8.6., and single aliquots of each ultrafiltrate were analyzed for radioactivity, as described in Section 2.8.9. The size of all aliquots were recorded.

Results:

In vitro blood-to-plasma partitioning ratios in humans were 0.31-0.34 over the concentration range of 5-500 ng/mL. In rat, mouse and dog, the partitioning ratios were 0.50-0.55, 0.46-0.58 and 0.44-0.52, respectively, over the concentration range of 10-10000 ng/mL. In vitro plasma protein binding of (S)-zopiclone in humans was 52.2-58.9% over the concentration range of 5-500 ng/mL. The protein binding values in the rat, mouse, and dog were 28.8-46.7, 36.7-56.5 and 31.9-43.5%, respectively over the concentration range of 10-10000 ng/mL.

6.4.3 Sepracor Study Document No. 2000-007. Evaluation of the effects of CYP450 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 inhibitors on S-zopiclone metabolism in human microsomes.

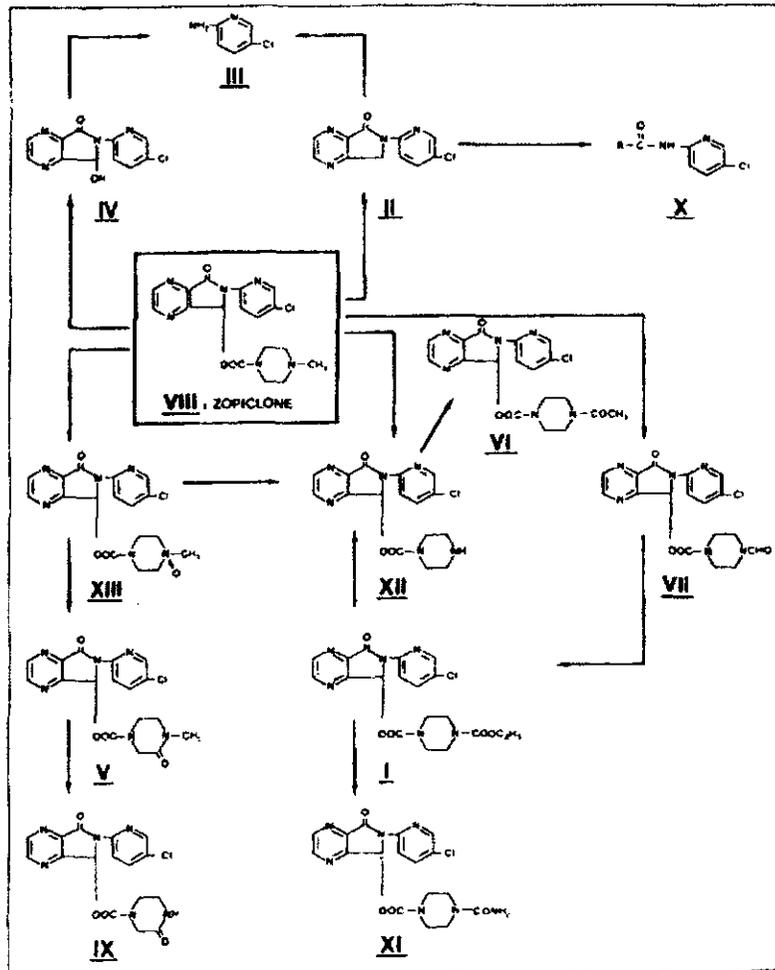
Objective:

To determine the relative contribution of different CYP450 isoforms to the metabolism of S-zopiclone and human liver microsomes in the presence or absence of selective P-450 isoform inhibitors.

Metabolic Scheme:

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CYP3A4 appears to be responsible for about 40% of both N-oxidation (XIII) and desmethylation (XII) of zopiclone while the CYP2E1 subfamily accounted for about 40% of N-desmethylation.

Methods:

Incubation Procedures

Main Study

Incubation mixtures were prepared in Tris buffer to contain 1 mg/mL microsomal protein, NADPH regenerating system (NRS), and either Tris only (negative

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control, NC), or one of the following P450 inhibitors: 5 μ M furafylline (CYP1A2), 250 μ M tranlycypromine (CYP2A6), 10 μ M omeprazole (CYP2C19), 1 μ M quinidine (CYP2D6), 100 μ M 4-methylpyrazole (CYP2E1), or 5 μ M ketoconazole (CYP3A4). After a 15-minute preincubation, (S)-zopiclone was added to each incubation mixture at each of 3 concentrations, and the incubation was continued for an additional 30 minutes. Incubation reactions were terminated with the addition of an equal volume of acetonitrile.

CYP2C8 Study

An additional experiment was conducted to assess the role of CYP2C8 in (S)-zopiclone metabolism. Incubation mixtures were prepared as described above using quercetin (100 μ M), a known inhibitor of CYP2C8, and (S)-zopiclone (10 μ M).

Control Incubations

Chromatographic Interference Control (CIC)

To investigate the possibility of chromatographic interference by each inhibitor and its metabolites, microsomes were preincubated with NADPH regenerating system (NRS) and each respective inhibitor for 15 minutes, then DMSO (10 μ L) was added to the samples and incubated for 30 minutes.

Metabolic Positive Control (MPC)

To determine the metabolic activity of the test system, microsomes were preincubated with NRS for 15 minutes, then spiked with 10 μ L of 100X 7-ethoxycoumarin (7-EC) solution and incubated for 30 minutes. The final 7-EC concentration was 100 μ M.

Metabolic Negative Control (MNC)

To detect the spontaneous formation of metabolites from a non-biological pathway, microsomal protein (1 mg/mL) was preincubated with Tris buffer for 15 minutes, then the test article was added (at the appropriate concentration). The incubation was continued for 30 minutes, then the reaction was terminated with acetonitrile.

Negative Control (NC)

To determine the specific effects of the test article as compared to the effects of the other controls on the test system, incubation mixtures were prepared in Tris buffer to contain 1 mg/mL microsomal protein, 1% DMSO, NRS, and the test article at each of the 3 tested concentrations for the main study, or a single concentration of 10 uM for the CYP2C8 study, then incubated for 30 minutes.

Results:

The esopiclone concentrations investigated, 10uM to 200uM, were within the range for those observed in the pharmacokinetic studies. The ketoconazole concentration was 5uM which is 5x the recommended concentration in the in vitro drug-drug interaction guidance page 5.

Table 47A: Control and test article metabolism in pooled human microsomes.

Test/Control Article	Conc. (uM)	Inhibitor ID	Conc. (uM)	(S)-Zopiclone (Parent)		
				Present (nmol)	Metabolized (nmol)	% of NC
(S)-Zopiclone	10	FUR	5	1.41 ± 0.26	5.87	172
	100		5	12.8 ± 1.7	74.5	121
	200		5	37.5 ± 7.1	136	116
	10	TRAN	250	1.57 ± 0.12	5.71	167
	100		250	17.5 ± 2.0	69.8	113
	200		250	49.6 ± 4.6	125	105
	10	SULF	50	1.35 ± 0.24	5.93	173
	100		50	15.7 ± 5.1	71.6	116
	200		50	40.1 ± 2.1	135	113
	10	OME	10	0.950 ± 0.170	6.33	185
	100		10	15.2 ± 2.0	72.1	117
	200		10	24.2 ± 13.4	151	127
	10	QUIN	1	1.47 ± 0.20	5.81	170
	100		1	17.7 ± 3.1	69.6	113
	200		1	69.0 ± 55.0	106	89.2
	10	4-METH	100	5.14 ± 0.32	2.14	62.6
	100		100	43.1 ± 14.2	44.2	71.5
	200		100	87.0 ± 32.0	88.0	74.0
	10	KTZ	5	4.81 ± 0.24	2.47	72.2
	100		5	60.4 ± 16.5	26.9	43.5
	200		5	98.8 ± 7.3	76.2	64.1

Values are mean ± standard deviation based on N = 3 replicates for experimental groups and N = 6 replicates for controls.

Abbreviations: Conc., concentration; NC, negative control; MNC, metabolic negative control; CIC, chromatographic interference control; NA, not applicable; FUR, furafylline; TRAN, tranalcypramine; SULF, sulfaphenazole; OME, omeprazole; QUIN, quinidine; 4-METH, 4-methylpyrazole; KTZ, ketoconazole.

* No cofactor present in MNC.

CYP2E1

The rate of parent disappearance for the test article decreased to 62.6, 71.5, and 74.01% of the NC at the tested concentrations of 10, 100 and 200 uM, respectively, in pooled human hepatocytes preincubated with 100 uM 4-methylpyrazole, selective inhibitor of CYP2E1. This indicates CYP2E1 may be responsible for the metabolism of (S)-zopiclone. (Table 1).

CYP3A4

The rate of parent disappearance for the test article decreased to 72.2, 45.5, and 64.09% of the NC at the tested concentrations of 10, 100 and 200 uM, respectively, in pooled human hepatocytes preincubated with 5 uM ketoconazole, selective inhibitor of CYP3A4. This indicates CYP3A4 may be responsible for the metabolism of (S)-zopiclone. (Table 1).

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6.3.4 Sepracor study No. 190-518. Determination of the inhibitory potential of (S)-zopiclone on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.

A — Study No. M-2000-010, 2000

Objective:

The purpose of this study was to determine the IC₅₀ of (S)-zopiclone against CYP450 isoforms. The specific-substrates used to determine the IC₅₀ of against CYP450 were 50 μM phenacetin (1A2), 50 μM coumarin (2A6), 75 μM tolbutamide (2C9), 50 μM S-mephenytoin (2C19), 8 μM dextromethorphan (2D6), 50 μM chlorzoxazone (2E1), and 50 μM testosterone (3A4).

Method: The isolated hepatocytes, prepared and pooled from 3 male and 2 female donors, were diluted with suspension media. Yield was counted and viability was measured using Trypan BlueTM exclusion. Each well of a 24-well plate contained 0.5 x 10⁶ cells (>70% viability) in a total final volume of 0.5 mL after the addition of the test article or known positive control. The samples were pre-incubated on an orbital shaker for 15 min. After the pre-incubation, appropriate 2X probe substrates (100X chlorzoxazone) were added to the groups, and the samples incubated for an additional 2 hours (1 hour for testosterone).

(S)-Zopiclone was added to the hepatocyte suspensions achieved final incubation concentrations of 1, 3.3, 10, 33.3, and 100 μM. The positive controls were incubated with hepatocytes at final concentrations of 10 μM furafylline (1A2), 50 μM diethyldithiocarbamate (2A6), 1 μM sulfaphenazole (2C9), 10 μM omeprazole (2C19), 1 μM quinidine (2D6), 100 μM 4-methylpyrazole (2E1), and 1 μM ketoconazole (3A4). A negative control was the incubation of hepatocytes with media.

The activity of the P450 isozymes was determined by measuring the rate of metabolism for the respective probe substrates. The activities were analyzed using HPLC method; metabolite production was quantified using internal standards and standard curves prepared in buffer.

Results: (S)-Zopiclone had no inhibitory effects on coumarin 7-hydroxylation (2A6), S-mephenytoin 4-hydroxylation (2C19), chlorzoxazone 6-hydroxylation (2E1), and 6α-testosterone (3A4). Dose-dependent inhibition with estimated IC₅₀ greater than the highest tested concentration of 100 μM was observed on 7-ethoxyresorufin O-dealkylation (1A2), tolbutamide 4-hydroxylation (2C9) and dextromethorphan O-demethylation (2D6).

Conclusion: (S)-Zopiclone did not inhibit the activities (IC₅₀) of CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in human hepatocytes.

6.3.5 Comparative in vitro metabolism in mouse, rat, dog and human hepatocytes

Sepracor Document 190-536. *In vitro* metabolism of (S)-zopiclone in freshly prepared mouse hepatocytes and cryopreserved male Sprague-Dawley rat hepatocytes, dog hepatocytes, and human hepatocytes — Study No. 00207, 2001

The purpose of this study was to compare the in vitro metabolism of (S)-zopiclone in animals and human hepatocytes in the absence or presence of (R)-zopiclone.

Method: [^{14}C](S)-zopiclone (50 and 100 μM for mouse, rat and dog, and 1 and 2 μM for human) and a mixture of [^{14}C](S)-zopiclone and (R)-zopiclone (50/50 μM for mouse, rat, and dog and 1/1 μM for human) were incubated with mouse, rat, dog, and human hepatocytes in a humidified incubator at 37°C and 95% O₂/5% CO₂ for 4 hours. Incubation was terminated by adding 2X volume of acetonitrile. After centrifugation to separate the supernatant and hepatocytes, 1 mL aliquot of the supernatant was evaporated to dryness and reconstituted in 300 μL of ACN:water (15:85) mixture. The reconstituted solution was immediately subjected for radio-HPLC profiling. The percent distribution of radioactivity was determined for [^{14}C](S)-zopiclone and its metabolites. Another aliquot of reconstituted solution was immediately analyzed by LC/(+)ESI-MS to characterize and/or identify zopiclone and its metabolites. A total of 14 regions, corresponding to [^{14}C](S)-zopiclone and its known and unknown metabolites, were integrated. Zopiclone and four metabolites, 2-amino-chloropyridine (APC), (S)-desmethyl zopiclone, zopiclone N-oxide, and lactamol, were confirmed by the comparison of — results between the incubation mixtures and respective standards.

Results: The radio-HPLC chromatograms showed the radioactivity profiles of [^{14}C](S)-zopiclone were very similar between the incubation mixtures with or without (R)-zopiclone in the mouse, rat, dog, and human hepatocytes. The percent distribution of radioactivity determined from radio-HPLC profiles were comparable for [^{14}C](S)-zopiclone and metabolites, desmethyl zopiclone, N-oxide zopiclone and lactamol. The percent of radioactivity for most of unknown metabolites was within 2% of [^{14}C](S)-zopiclone incubation dose with the exception that the degradation products/metabolites, observed in both K-H buffer and incubation mixtures at R_t — , accounted for 19.03-23.80% of the total radioactivity after 4 h incubation.

Conclusion: The results suggested that (R)-zopiclone imposed no significant effects on the in vitro metabolism of [^{14}C](S)-zopiclone in mouse, rat, dog, and human hepatocytes.

6.5 IN VIVO DRUG INTERACTION STUDIES

6.5.1 Individual Study Report- PHARMACOKINETIC INTERACTION STUDY BETWEEN (S)-ZOPICLONE AND KETOCONAZOLE -PROTOCOL NO.: 190-023

Introduction

Ketoconazole, a broad-spectrum antifungal agent, is known to be a potent inhibitor of the CYP3A4 enzyme system and affects the metabolism of a variety of drugs including cyclosporine, phenytoin and warfarin. *In vitro* data suggests that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. The most frequent adverse reactions reported were nausea and vomiting in approximately 3%, abdominal pain in 1.2 %, and pruritis in 1.5%. Rare cases of fatal hepatotoxicity have been reported related to ketoconazole therapy. These have been uncommon at the starting dose, but occur more frequently if dose escalation is required for clinical reasons. Esopiclone is not a substrate for p-glycoprotein (pGp). However, *in vitro* metabolism data have shown esopiclone to be a substrate for CYP3A4, consequently an *in vivo* drug-drug interaction may occur. Because ketoconazole is known to be a potent inhibitor of the CYP3A4 enzyme system and affects the metabolism of a variety of drugs, this trial was conducted to study the pharmacokinetic interaction of esopiclone and ketoconazole.

Objectives

To evaluate the pharmacokinetic interaction of multiple oral doses of 3 mg of esopiclone with multiple doses of 400 mg of ketoconazole in healthy volunteers.

Study Design

This was a single-center, inpatient, three-way crossover, open-label, multiple dose study. Subjects were randomized to receive a sequence of the following treatments: 400 mg of ketoconazole (2 x 200 mg tablets) daily for five days (Treatment A), 3 mg esopiclone (2 x 1.5 mg tablets) daily for five days (Treatment B), or 3 mg of esopiclone (2 x 1.5 mg tablets) co-administered with 400 mg of ketoconazole (2 x 200 mg tablets) daily for five days (Treatment C). Eighteen subjects were enrolled. Up to 24 subjects were allowed. Six treatment sequences were used (ABC, ACB, BAC, BCA, CAB, and CBA), with three of the eighteen subjects randomized to each sequence. A 14-day washout period was scheduled between each treatment sequence.

Demographics

Table 48A: Demographic and Baseline Characteristics

Characteristic	Statistic	Treatment Sequence						All Subjects (n=18)
		ABC (n=3)	BCA (n=3)	CAB (n=3)	BAC (n=3)	CBA (n=3)	ACB (n=3)	
Age	Mean (yr)	32.0	28.7	35.3	39.3	49.3	35.7	36.7
	SD (yr)	10.6	11.5	12.1	11.7	13.3	18.6	13.0
	Min, Max	24, 44	22, 42	26, 49	26, 48	38, 64	23, 57	22, 64
Gender								
Male	n (%)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	3 (100.0)	1 (33.3)	12 (66.7)
Female	n (%)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	2 (66.7)	6 (33.3)
Race								
Caucasian	n (%)	3 (100.0)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	3 (100.0)	14 (77.8)
Black	n (%)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	4 (22.2)
Height	Mean (cm)	178.3	171.5	171.8	176.1	177.7	171.8	174.5
	SD (cm)	11.1	12.6	5.9	15.3	9.4	9.2	9.7
	Min, Max	166, 185	158, 182	165, 176	160, 191	170, 188	167, 183	158, 191
Weight	Mean (kg)	82.7	74.9	78.3	77.0	79.8	73.1	77.6
	SD (kg)	12.8	18.3	6.5	15.5	5.8	6.0	10.5
	Min, Max	70, 95	54, 89	72, 85	60, 89	74, 86	66, 77	54, 95

Dose Selection:

Ketoconazole has been used in many clinical studies at the dose of 400 mg per day given in divided doses. It has been shown to be well tolerated and safe at this dose. At 400 mg per day there is almost complete inhibition of CYP3A4.

Dosing was at 8:00 am.

Sample Collection and Handling

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Visit 1 Screening Visit	Up to 21 Days	Visit 2 Day -1 to Day 7 Dose (Days 1-5) ^a	Washout 14 Days	Visit 3 Day -1 to Day 7 Dose (Days 1-5) ^a	Washout 14 Days	Visit 4 Day -1 to Day 7 Dose (Days 1-5) ^a
<ul style="list-style-type: none"> -Informed Consent -ECG, Vital Signs -Clinical Labs -Medical/Psychiatric History -Physical Examination -Romberg Neurological Exam -Heel-To-Toe Gait Test -UDS/Cotinine -Serum Pregnancy Test (females only) -Hepatitis B and C testing 		<ul style="list-style-type: none"> -ECG, Vital Signs -Clinical Labs -Physical Examination -Romberg Neurological Exam -Heel-To-Toe Gait Test -UDS/Cotinine -Urine Pregnancy Test (females of Childbearing potential only) -AE/ Concom Med Monitoring -Serial PK assessments 		<ul style="list-style-type: none"> -Vital Signs -Physical Examination -Clinical Labs -Romberg Neurological Exam -Heel-To-Toe Gait Test -UDS/Cotinine -Urine Pregnancy Test (females of childbearing potential only) -AE/ Concom Med Monitoring -Serial PK assessments 		<ul style="list-style-type: none"> -ECG, Vital Signs -Clinical Labs -Physical Examination -Romberg Neurological Exam -Heel-To-Toe Gait Test -UDS/Cotinine -Urine Pregnancy Test (females of Childbearing potential only) -AE/ Concom Med Monitoring -Serial PK assessments

^a Eighteen subjects were randomized to receive one of six selected treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA) over the three study visits (1, 2 and 3), with the three treatments defined as follows.

A = ketoconazole 400 mg (administered as two 200 mg tablets) daily for 5 days

B = esopiclone 3 mg (administered as two 1.5 mg tablets) daily for 5 days

C = esopiclone 3 mg daily in combination with ketoconazole 400 mg daily for 5 days

Serial blood draws for PK analysis were performed at +0.5, +1, +1.5, +2, +3, +4, +6, +8, +12, +16 Day 5 after dosing. PK blood draws were also obtained +24, +30, and +36 hours (i.e., Day 6) after dosing and at 48 hours after dosing (i.e., Day 7).

Bioanalytical Methods-

Studied Period : Clinical Conduct October 12, 2000- December 20, 2000

Analysis of plasma samples for eszopiclone were conducted from —

Analysis of plasma samples for ketaconazole were conducted from —

Theoretical Storage time: — for eszopiclone and ketaconazole.

	Eszopiclone	Ketaconazole
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		

Comments:

1. The analytical limit for run —) was set at — since the — standards could not be analyzed.
2. The firm also seeded ketoconazole samples with eszopiclone and desmethylzopiclone and showed that there was no interference.

Statistical Analysis

For each analyte, the following PK parameters were determined:

- C_{max} Maximum observed concentration.
- t_{max} Time of occurrence of C_{max}.
- C_{last} The last post-dose quantifiable concentration.

- t_{last} The time of the last post-dose quantifiable concentration.
- λ_z Elimination rate constant
- $t_{1/2}$ Terminal phase half-life, calculated as $\ln(2)/\lambda_z$.
- AUC(0-last) Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration
- τ Nominal dosing interval.
- AUC(0- τ) Area under the plasma concentration time curve over the dosing interval (τ).

If the last plasma concentration for the dosing interval was BLQ, then AUC(0- τ) was calculated up to the time of the last quantifiable concentration during the dosing interval; if, however, the time of this last concentration was substantially less than τ , then AUC(0- τ) may have been considered to be missing, at the discretion of the pharmacokineticist.

AUC(0- ∞) Area under the plasma concentration-time curve for the 0-infinity interval, calculated by summing the area under the curve from time zero to the time of the last quantifiable concentration (t_{last}) and the extrapolated AUC from t_{last}

The verification of achievement of steady-state was accomplished by examination of the graphical display of mean trough esopiclone, (S)-desmethylzopiclone, and ketoconazole concentrations over time, and this estimation was guided by statistical testing.

RESULTS

Table 49A: Mean Esopiclone Plasma Concentration Over Time Following Multiple Oral Administration of 3 mg Esopiclone Monotherapy or in Combination with 400 mg Ketoconazole

Visit (day)	Time (hr)	N	Esopiclone Concentration (ng/ml)			
			Esopiclone		Esopiclone + Ketoconazole	
			Mean	SD	Mean	SD
1	Pre-dose	18	BLQ	-	BLQ	-
2	Pre-dose	18	1.94	1.13	5.84	3.25
3	Pre-dose	18	2.04	1.23	8.51	4.91
4	Pre-dose	18	2.33	1.41	9.33	5.00
5	Pre-dose	18	2.52	1.39	9.92	5.86
	0.5	17	32.68	14.19	43.27	18.71
	1	17	35.18	6.31	52.96	14.81
	1.5	17	31.22	5.44	49.85	13.10
	2	17	29.11	4.92	47.97	9.95
	3	17	24.21	4.75	43.17	12.72
	4	17	20.39	4.89	39.09	12.39
	6	17	16.09	4.12	34.37	11.45

	8	17	12.08	4.09	29.33	9.68
	12	17	7.21	2.60	21.27	8.35
	16	17	4.63	1.88	15.66	6.23
6	24	17	2.29	1.29	9.70	5.30
	30	17	BLQ	-	5.95	3.82
	36	17	BLQ	-	3.62	2.74
7	48	17	BLQ	-	1.53	1.79

BLQ: Below limit of quantification

Table 50A: Esopiclone Pharmacokinetic Parameters (Mean \pm SD) Following Multiple Oral Administration of 3 mg Esopiclone Monotherapy or in Combination with 400 mg Ketoconazole

Parameter	Mean \pm SD			
	N	Esopiclone	N	Esopiclone + Ketoconazole
C _{max} (ng/ml)	17	39.84 \pm 8.60	18	56.81 \pm 14.63
AUC(0- τ) (hr*ng/ml)	17	260.95 \pm 64.05	18	588.23 \pm 196.03
AUC(0-last) (hr*ng/ml)	17	270.93 \pm 75.07	18	690.35 \pm 268.53
AUC(0- ∞) (hr*ng/ml)	17	286.45 \pm 79.47	18	724.69 \pm 293.83
t _{1/2} (hr)	17	7.21 \pm 1.25	18	9.44 \pm 2.12
t _{max} ^a (hr)	17	1.00 (0.38-2.05)	18	1.00 (0.50-2.00)
^a t _{max} is presented as median (range)				

Table 51A: Treatment Comparison of Esopiclone Pharmacokinetic Parameters

Parameter	Treatment	N	Geometric Combination versus Monotherapy		
			LS Mean	Ratio (%)	90% CI
AUC _(0-τ) (hr*ng/ml)	Esopiclone	17	250.8	-	-
	Esopiclone + Ketoconazole	18	563.3	224.63	(208.5, 242.0)
C _{max} (ng/ml)	Esopiclone	17	38.6	-	-
	Esopiclone + Ketoconazole	18	55.2	143.09	(130.0, 157.5)
t _{1/2} (hr)	Esopiclone	17	7.0	-	-
	Esopiclone +	18	9.2	131.83	(124.7, 139.4)

	Ketoconazole				
tmax ^a (hr)	Esopicone	17	1.0	-	-
	Esopicone + Ketoconazole	18	1.0	-	-
^a tmax is rank-transformed and median is presented instead of geometric LSmean.					

Table 52A: Mean Ketoconazole (Substrate) Concentrations Over Time Following Multiple Oral Administration of 400 mg Ketoconazole Monotherapy or in Combination with 3 mg Esopicone (Interacting Drug).

Day	Time (hr)	Ketoconazole Concentration (µg/ml)					
		Ketoconazole			Esopicone + Ketoconazole		
		N	Mean	SD	N	Mean	SD
1	Pre-dose	18	BLQ	-	18	BLQ	-
2	Pre-dose	18	BLQ	-	18	BLQ	-
3	Pre-dose	18	0.19	0.17	18	0.23	0.23
4	Pre-dose	18	0.27	0.28	18	0.35	0.32
5	Pre-dose	18	0.28	0.22	18	0.33	0.29
	0.5	18	2.58	1.41	18	2.80	1.69
	1.0	18	6.76	2.95	18	5.75	2.50
	1.5	18	8.36	2.53	18	6.53	2.36
	2.0	17	9.29	3.05	18	7.41	2.73
	3.0	18	7.84	2.60	18	6.75	2.67
	4.0	18	6.88	2.47	18	6.15	2.31
	6.0	18	5.50	2.34	18	4.95	2.05
	8.0	18	4.16	2.11	18	3.71	1.57
	12.0	18	2.27	1.50	18	1.98	1.14
	16.0	18	1.20	0.98	18	1.02	0.72
6	24.0	18	0.42	0.39	18	0.38	0.34
	30.0	18	0.18	0.18	18	0.19	0.19
	36.0	18	0.08	0.09	18	0.09	0.10
7	48.0	18	BLQ	-	18	BLQ	-

BLQ: Below limit of quantification

Table 53A: Ketoconazole Pharmacokinetic Parameters (Mean ± SD) Following Multiple Oral Administration of 400 mg Ketoconazole Monotherapy or in Combination with 3 mg Esopicone

Parameter	N	Ketoconazole	Mean ± SD	Esopicone + Ketoconazole
			N	
Cmax (µg/ml)	18	9.58 ± 3.02	18	7.99 ± 2.76

AUC(0-τ) (hr*μg/ml)	18	75.63 ± 32.88	18	65.73 ± 27.15
AUC(0-last) (hr*μg/ml)	18	78.67 ± 35.63	18	68.64 ± 29.23
AUC(0-∞) (hr*μg/ml)	18	79.5 ± 35.76	18	69.59 ± 29.52
T ½ (hr)	18	5.90 ± 3.51	18	6.00 ± 3.07
tmax ^a (hr)	18	2.00 (—)	18	2.00 (—)
^a Expressed as median (range).				

Table 54A: Treatment Comparison of Ketoconazole Pharmacokinetic Parameters

Parameter	Treatment	N	Combination versus Monotherapy Comparison		
			Geometric LS Mean	Ratio (%)	90% CI
AUC(0-τ) (hr*μg/ml)	Ketoconazole	18	68.3	-	-
	Esopiclone + Ketoconazole	18	59.7	87.51	(73.7, 103.9)
Cmax (μg/ml)	Ketoconazole	18	9.1	-	-
	Esopiclone + Ketoconazole	18	7.4	81.95	(70.9, 94.7)
t1/2 (hr)	Ketoconazole	18	5.2	-	-
	Esopiclone + Ketoconazole	18	5.4	102.92	(90.1, 117.5)
tmax ^a (hr)	Ketoconazole	18	2.0	-	-
	Esopiclone + Ketoconazole	18	2.0	-	-

^a tmax is rank-transformed and median is presented instead of geometric LSmean.

Comments:

1. Systemic exposure (AUC(0-τ)) to esopiclone was increased on average by approximately 2.2 fold for the esopiclone co-administered with ketoconazole group when compared to the esopiclone monotherapy group. The maximum concentration of esopiclone with the combination treatment was approximately 43% greater on average than the C_{max} achieved by esopiclone monotherapy. Half-life increased 2 hrs in the presence of ketoconazole.

2. The maximum concentration of ketoconazole attained with the combination treatment was approximately 17% lower on average than C_{max} achieved by ketoconazole monotherapy. Systemic exposure (AUC(0-τ)) to ketoconazole was also slightly reduced by approximately

12% following the co-administration with esopiclone when compared to ketoconazole monotherapy.

3. There is the possibility that the drug effect of ketoconazole on eszopiclone (i.e., greater systemic exposure) may be exacerbated due to a diurnal effect which the firm has not investigated since dosing was done at 8:00am.

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6.5.2 Individual Study Report- PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION STUDY BETWEEN (S)-ZOPICLONE AND (R,S)-WARFARIN IN HEALTHY SUBJECTS -PROTOCOL NO.: 190-021

Study Introduction

(R,S)-Warfarin is a widely prescribed anticoagulant that is indicated for the prophylaxis and treatment of venous thrombosis, thromboembolic complications associated with atrial fibrillation and cardiac valve replacement, and is indicated to reduce recurrent myocardial infarction. (R,S)-Warfarin is rapidly absorbed after oral administration with peak concentrations reached within the first 4 hours. At steady state, the half-life of (S)-warfarin is 21-43 hours and of (R)-warfarin is 79-83 hours.

The results of an in vitro CYP450 study indicated that esopiclone would not be expected to affect the metabolism of (R,S)-warfarin. Nevertheless, an in vivo pharmacokinetic / pharmacodynamic interaction study was initiated in healthy subjects because (R,S)-warfarin has a narrow therapeutic index and in vitro studies are not always predictive of in vivo results. The current study evaluated the pharmacodynamic and pharmacokinetic interactions of multiple doses of esopiclone on a single dose of (R,S)-warfarin in healthy volunteers.

STUDY OBJECTIVES

Primary:

To evaluate the pharmacodynamic effect (interaction) of multiple doses of esopiclone on a single dose of (R,S)-warfarin in healthy volunteers.

Secondary:

To evaluate the pharmacokinetic effect (interaction) of multiple doses of esopiclone on a single dose of (R,S)-warfarin in healthy volunteers.

Study Design

This was a single-center, in- and out-patient, randomized, multiple daytime dosing, complete cross-over, two-treatment, open-label study in healthy adults. Subjects were randomized to receive one of the following treatment sequences AB or BA in a crossover fashion with a 14-day washout between treatments.

Appears This Way
On Original

Treatment Sequence	Visit 2	Visit 3
I	(R,S)-Warfarin Single 25 mg dose (Treatment A)	5x daily doses of 3 mg esopiclone, with (R,S)-warfarin 25 mg dose in combination with the last esopiclone dose (Treatment B)
II	5x daily doses of 3 mg esopiclone, with (R,S)-warfarin 25 mg dose in combination with the last esopiclone dose (Treatment B)	(R,S)-Warfarin Single 25 mg dose (Treatment A)

Sample Collection and Handling

Plasma samples, analyzed for (R,S)-warfarin, were drawn from subjects after dosing with (R,S)-warfarin alone and after dosing with (R,S)-warfarin in combination with esopiclone at the following times: at pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours post-dosing. Plasma samples, analyzed for esopiclone, were drawn from subjects prior to dosing with esopiclone on Visit 3, Days 17, 18, and 19 for Treatment Sequence I and on Visit 2, Days 3, 4, and 5 for Treatment Sequence II.

Pharmacodynamic Sampling for PT/INR(prothrombin time and international normalization ratio)

Visit 2 (days -1, 1, 2,3,4,5,6,7)

day 1- 2, 6, 8, and 12 hrs)

day2-24 hrs

day3-48 hrs

day4-72 hrs

day5-96 hrs

day6-120hrs

day7-144hrs

The same sampling pattern was followed on Visit 3(days 14-22).

Demographics-

Demographic and Baseline Characteristics				
(All Subjects Who Received Study Drug)				
		Treatment Sequence		
		All Subjects	AB	BA
Characteristic	Statistic	(N=12)	(N=6)	(N=6)
Age (yrs)	N	12	6	6
	Mean	37.8	33.0	42.5
	Std Dev	14.1	15.4	12.2

	Median	34.0	27.5	49.5
	Min	21	21	24
	Max	62	62	51
Gender				
Male	n (%)	8 (66.7%)	5 (83.3%)	3 (50.0%)
Female	n (%)	4 (33.3%)	1 (16.7%)	3 (50.0%)
Race				
Caucasian	n (%)	6 (50.0%)	2 (33.3%)	4 (66.7%)
Black	n (%)	5 (41.7%)	3 (50.0%)	2 (33.3%)
Asian	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	n (%)	1 (8.3%)	1 (16.7%)	0 (0.0%)
Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)	N	12	6	6
	Mean	174.6	175.3	173.8
	Std Dev	8.6	8.6	9.3
	Median	174.3	175.3	174.3
	Min	162	166	162
	Max	186	185	186
Weight (kg)	N	12	6	6
	Mean	76.3	77.7	74.9
	Std Dev	11.7	13.3	10.9
	Median	74.7	78.6	74.7
	Min	60	60	61
	Max	95	95	93

Note: A=Single administration of 25 mg Warfarin. B=Single administration of in combination with 3 m g (S)-zopiclone following four once daily 3 m g dos zopiclone.

(R,S)-Warfarin is marketed for anticoagulation. In drug-interaction studies with other currently marketed hypnotic drugs, 25 mg doses of (R,S)-warfarin have been used without warfarin-related adverse events.

Study medication was administered at approximately 08:00 of dosing day. Subjects took study medication, with water after fasting approximately 9 hours .

Material	Manufacturer	Lot Number(s)
(S)-Zopiclone 1.5 mg tablets		F0410001
Coumadin ((R,S)-warfarin) 25 mg	/	
10 mg tablets		ENF381A
5 mg tablet		ENE256A

Bioanalytical Methods-

Studied Period (years): Clinical Conduct September 21, 2000 to November 2, 2000

Analysis of plasma samples was conducted from

Theoretical Storage time: 3 months

	R-Warfarin	S-Warfarin
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		
Stability		
Recovery		
15 ng/ml		
250 ng/ml		
800 ng/ml		
Freeze-Thaw		

The firm has also conducted studies to show that eszopiclone does not interfere with the analysis of warfarin.

Statistical Analysis

The primary outcome variable was the pharmacodynamic parameter:

INR International Normalization Ratio=(Patient PT/Mean Normal PT)^{ISI}

Where ISI=International Sensitivity Index

AUC_{INR} Area under the INR-time curve from time zero (t1) to the time of the last post-dose INR value

The INR is for anticoagulant monitoring.

INR_{max} = Also known as E_{max}, was the largest INR (effect) value observed.

INR_{tmax} = Also known as t_{max}, was the time at which the INR_{max} occurred.

The pharmacokinetic variables included the following for (R)- and (S)-warfarin:

C_{max}	Maximum observed concentration.
t_{max}	Time of occurrence of C_{max} .
C_{last}	The last post-dose quantifiable concentration.
t_{last}	The time of the last post-dose quantifiable concentration
λ_z	Elimination rate constant
$t_{1/2}$	Terminal phase half-life
AUC(0-last)	Area under the plasma concentration-time curve from time zero (t_1) to the time of the last post-dose quantifiable plasma concentration
AUC(0- ∞)	Area under the plasma concentration-time curve for the 0-infinity interval.

Initially, trough values from Days 17, 18, 19 (Treatment Sequence I) or Days 3, 4, 5 (Treatment Sequence II) were included in the analysis. The null hypothesis that the slope of the line through the time points was zero was tested at the two sided 10% significance level. If the null hypothesis was rejected, then a test for linear trend would be conducted with the first time point removed from the contrast. If the null hypothesis was still rejected, it would be concluded that steady-state was not obtained. The steady-state trough concentration was estimated using the observed mean for all time points in the final linear trend test.

RESULTS

Table 55A: Mean \pm SD (R)- and (S)-Warfarin Plasma Concentration Over Time Following Oral Dosing of (R,S)-Warfarin or the Combination of (R,S)-Warfarin plus Esopiclone

Time post-dose (hr)	Treatment			
	(R,S)-Warfarin (25 mg)		+ Esopiclone (3 mg)	
	(R)-warfarin (ng/mL)	(S)-warfarin (ng/mL)	(R)-warfarin (ng/mL)	(S)-warfarin (ng/mL)
Pre-dose	10.0 \pm 12.4*	5.5 \pm 7.5*	5.3 \pm 7.3*	BLQ
0.5	1394.7 \pm 553.8	1477.9 \pm 592.7	1193.7 \pm 544.0	1287.8 \pm 596.9
1	1693.9 \pm 463.4	1740.0 \pm 457.3	1449.3 \pm 385.3	1496.6 \pm 391.5
1.5	1544.3 \pm 368.7	1553.3 \pm 390.4	1449.8 \pm 415.0	1440.3 \pm 378.9
2	1491.4 \pm 313.2	1500.5 \pm 313.8	1466.0 \pm 356.9	1458.3 \pm 333.1
3	1246.1 \pm 207.9	1247.9 \pm 225.0	1239.6 \pm 254.7	1231.2 \pm 246.2
4	1192.5 \pm 218.7	1182.9 \pm 230.3	1241.8 \pm 251.0	1217.6 \pm 241.0
6	1200.3 \pm 264.0	1137.3 \pm 271.9	1154.4 \pm 258.0	1099.8 \pm 249.1
8	1136.3 \pm 177.6	1032.9 \pm 185.8	1123.8 \pm 210.3	1013.4 \pm 189.3

12	1042.8 ± 172.3	903.5 ± 175.9	1124.5 ± 200.6	962.8 ± 185.8
24	944.8 ± 308.7	752.7 ± 232.0	928.4 ± 175.3	734.3 ± 178.8
48	614.3 ± 143.7	427.8 ± 148.1	612.7 ± 164.2	424.1 ± 155.5
72	414.3 ± 146.2	244.1 ± 107.1	428.8 ± 116.8	254.5 ± 110.8
96	312.5 ± 122.2	172.6 ± 98.2	273.0 ± 99.7	147.9 ± 76.6
120	218.9 ± 97.4	106.0 ± 59.5	182.2 ± 94.9	96.1 ± 69.4
144	165.4 ± 77.7	75.7 ± 43.7	141.6 ± 79.2	70.3 ± 47.5

* - There was residual carryover from previous treatment sequence.

Table 56A: Descriptive Statistics of Pharmacokinetic Parameters for (R)-Warfarin Following Oral Dosing of (R,S)-Warfarin or the Combination of (R,S)-Warfarin plus Esopiclone

Parameter	Treatment (n=12)	Mean ± SD	Geometric Least Squared Mean	Treatment Comparisons ¹⁾		
				Ratio of Geometric Least Squared Means	90% CI	p-value
C _{max} (ng/mL)	(R,S)-warfarin	1813.3 ± 367.6	1782.2	91.1	(82.5, 100.6)	0.1208
	(R,S)-warfarin + esopiclone	1666.8 ± 381.0	1623.9			
AUC _(0-12h) (hr*ng/mL)	(R,S)-warfarin	77136.8 ± 18559.1	75309.0	98.2	(93.7, 102.8)	0.4869
	(R,S)-warfarin + esopiclone	75384.1 ± 16335.7	73936.8			
AUC _(0-∞) (hr*ng/mL)	(R,S)-warfarin	90021.1 ± 26031.4	87052.8	94.6	(90.1, 99.3)	0.0665
	(R,S)-warfarin + esopiclone	84744.0 ± 22784.2	82352.0			
t _{max} (hr)	(R,S)-warfarin	1.0 ; — ; 1 ^A	-	-	-	0.5848
	(R,S)-warfarin + esopiclone	1.0 ; — ; 1 ^A	-			
t _{1/2} (hr)	(R,S)-warfarin	50.8 ± 11.0	49.7	82.2	(70.0, 96.5)	0.0509
	(R,S)-warfarin + esopiclone	43 ± 14.1	40.8			

¹⁾ Median [Range] instead of Mean ± SD

Table 57A: Descriptive Statistics of Pharmacokinetic Parameters for (S)-Warfarin Following Oral Dosing of (R,S)-Warfarin or the Combination of (R,S)-Warfarin Plus Esopiclone

Parameter	Treatment (n=12)	Mean ± SD	Geometric Least Squared Mean	Treatment Comparisons ^B		
				Ratio Geometric Least Squared Means	90% CI	p-value
C _{max} (ng/mL)	(R,S)-warfarin	1884.2 ± 391.0	1850.5	91.2	(81.9, 101.5)	0.1493
	(R,S)-warfarin + esopicone	1736.7 ± 420.3	1687.2			
AUC _(0-12h) (hr*ng/mL)	(R,S)-warfarin	56445.3 ± 15894.4	54584.2	98.6	(92.6, 104.9)	0.6859
	(R,S)-warfarin + esopicone	55480.3 ± 14575.4	53809.8			
AUC _(0-∞) (hr*ng/mL)	(R,S)-warfarin	60748.4 ± 18639.3	58383.3	97.4	(91.7, 103.4)	0.4451
	(R,S)-warfarin + esopicone	59080.3 ± 17503.8	56859.0			
t _{max} (hr)	(R,S)-warfarin	1.0 ^A	-	-	-	0.1970
	(R,S)-warfarin + esopicone	1.0 ^A	-			
t _{1/2} (hr)	(R,S)-warfarin	37.5 ± 7.7	36.7	86.9	(76.4, 98.8)	0.0758
	(R,S)-warfarin + esopicone	33.2 ± 9.9	31.9			

^A Median [Range] instead of Mean ± SD

Table 58A: Descriptive Statistics and Treatment Comparisons of Pharmacodynamic Parameters Following Oral Dosing of (R,S)-Warfarin or the Combination of (R,S)-Warfarin plus Esopicone

Parameter	Treatment (n=12)	Mean ± SD	Geometric Least Squared Mean	Treatment Comparison ^B		
				Ratio of Geometric Least Squared Means	90% CI	p-value
AUC _{INR} (hr*INR)	(R,S)-warfarin	219.9 ± 42.9	216.6	102.4	(98.6, 106.3)	
	(R,S)-warfarin + esopicone	223.3 ± 28.3	221.7			
INR _{max} (INR)	(R,S)-warfarin	2.1 ± 0.7	2.0	103.9	(96.9, 111.4)	
	(R,S)-warfarin + esopicone	2.1 ± 0.5	2.1			
INR _{max} (hr)	(R,S)-warfarin	48.0 ^A	-	-	-	0.5848
	(R,S)-warfarin + esopicone	48.0 ^A	-			

^A Median [Range] instead of Mean ± SD

Comments

1. The pharmacokinetics of (R)-warfarin following a single dose (R,S)-warfarin given alone were not statistically significantly different to those following a single dose of (R,S)-warfarin given in combination with esopiclone at steady state. The 90% confidence intervals of ratios of geometric least squared means of a single dose of (R,S)-warfarin given with esopiclone to a single dose of (R,S)-warfarin alone for $AUC_{(0-last)}$ (93.7%, 102.8%) and C_{max} (82.5%, 100.6%) fell between 80 and 125%.

2. The pharmacokinetics of (S)-warfarin following a single dose (R,S)-warfarin given alone were not statistically significantly different to those following a single dose of (R,S)-warfarin given in combination with esopiclone at steady state. The 90% confidence intervals of ratios of geometric least squared means of a single dose of (R,S)-warfarin given with esopiclone to a single dose of (R,S)-warfarin alone for $AUC_{(0-last)}$ (92.6%, 104.9%) and C_{max} (81.9%, 101.5%) fell between 80 and 125%.

3. For AUC_{INR} and INR_{max} , the 90% confidence intervals for the ratios of geometric least squared means of (R,S)-warfarin in combination with esopiclone to (R,S)-warfarin alone were lying between 80 and 125% (and the original limits of 70% to 143% as set in the protocol). INR_{max} was not significantly different following (R,S)-warfarin in combination with esopiclone as compared to a single dose (R,S)-warfarin alone.

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**6.5.3 Individual Study Report- PHARMACOKINETIC INTERACTION STUDY
BETWEEN (S)-ZOPICLONE AND DIGOXIN IN HEALTHY SUBJECTS
PROTOCOL NO.: 190-022**

Study Introduction

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. Digitalis is being prescribed for congestive heart failure, paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter. Following oral administration, peak serum concentrations of digoxin occur at 1 to 3 hours. Digoxin has a half-life of 1.5 to 2 days. Commonly observed adverse events include arrhythmia, fatigue, generalized muscle weakness, agitation, hallucination, anorexia, nausea, yellow-green halos around visual images and blurred vision. Less frequently occurring adverse events include headache, dizziness, vertigo, stupor, paresthesia, light flashes, photophobia, diplopia, vomiting and diarrhea. Digoxin produces PR prolongation and ST segment depression, which should not by themselves be considered digoxin toxicity. There are no published data that address the interaction of either (S)- or (R,S)-zopiclone with digoxin. Because digoxin is commonly used in the adult population, this trial was conducted to study the pharmacokinetic interaction of (S)-zopiclone and digoxin at steady state.

Objectives:

The primary objective was to evaluate the pharmacokinetic interaction of a single oral dose of 3 mg (S)-zopiclone and digoxin at steady state in healthy volunteers.

Study Design

This was a single-center, in-patient, open label, multi-daytime-dose study in healthy male and female subjects between the ages of 21 and 64, inclusive. Twelve subjects were enrolled and received two 0.5 mg doses of digoxin on Day 1, taken 12 hours apart, followed by single daily doses of 0.25 mg digoxin from Day 2 through Day 7. On Day 7, subjects received digoxin in combination with a single 3 mg oral dose of clinical service formulation (S)-zopiclone. Pharmacokinetic and safety assessments were collected throughout the study and continued until at least 24 hours post-dose of the combination treatment. All medications were taken with 240 mL of water.

Digoxin (Lanoxin[®]) is a marketed compound and the dosing regimen of 1 mg loading dose and 0.25 mg daily maintenance dose has been reported to be well tolerated.

Table 59A: Subject Demographics

	All Subjects (N=12)
Age	
Mean (SD) years	40.7 (13.8)
Min, Max	24, 64
Gender	
Male; n (%)	7 (58.3%)
Female; n (%)	5 (41.7%)
Race	
Caucasian; n (%)	11 (91.7%)
Black; n (%)	1 (8.3%)
Asian; n (%)	0 (0.0%)
Hispanic; n (%)	0 (0.0%)
Other; n (%)	0 (0.0%)
Height; mean (SD) cm	171.2 (6.9)
Weight; mean (SD) kg	70.9 (12.3)
BMI; mean (SD) kg/m ²	24.1 (3.4)

Sample Collection and Handling

Plasma digoxin pharmacokinetic samples were drawn at Day 1 (baseline) and pre-dose on Days 4 through 7. On Days 6 and 7, digoxin pharmacokinetic samples were collected at +1, +2, +4, +6, +8, and +12 hours post-dosing. On Day 8, a final plasma sample was collected at 24 hours post the final dose (Day 7) for digoxin pharmacokinetic sampling.

Bioanalytical Methods-

Studied Period (years): Clinical Conduct October 4, 2000-October 26, 2000

Analysis of plasma samples was conducted from _____

Theoretical Storage time: _____

Method	Immunoassay
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%)	
Accuracy of QC Samples (%)	
Recovery	

Statistical Analysis

The following pharmacokinetic parameters were determined for digoxin at steady state for each treatment:

- C_{max} Maximum observed concentration.
- t_{max} Time of occurrence of C_{max} .
- C_{last} The last post-dose quantifiable concentration (see note below). t_{last}
The time of the last post-dose quantifiable concentration.
- λ_z Elimination rate constant for the terminal phase
- $t_{1/2}$ Terminal half-life, calculated as $\ln(2)/\lambda_z$.

AUC(0-last)	Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration
τ	Nominal dosing interval.
AUC(0-t)	Area under the plasma concentration time curve over the dosing interval (t).
AUC(0-∞)	Area under the plasma concentration-time curve for the 0-infinity interval .

The verification of steady-state trough concentrations was accomplished by examination of the graphical display of mean digoxin trough concentrations (C24hr) over time but this verification was guided by statistical testing. Trough concentrations were defined as pre-dose digoxin concentrations obtained on Days 4 through 7. The statistical analysis was conducted via a step-wise procedure to test for linear trend using contrasts in an analysis of variance (ANOVA) model containing terms for subject and day effects.

RESULTS

Table 60A: Mean ± SD Plasma Concentration (ng/mL) of Digoxin at Steady-State by Treatment (n=12)

Time Post-Dose (hr)	Digoxin alone (Day 6)		(S)-Zopiclone + Digoxin (Day 7)	
	Mean	SD	Mean	SD
Pre-dose	0.71	0.14	0.72	0.16
1	2.32	0.62	1.96	0.60
2	1.82	0.45	1.79	0.43
4	1.10	0.24	1.20	0.21
6	0.82	0.12	0.89	0.09
8	0.78	0.11	0.78	0.07
12	0.68	0.11	0.66	0.08
24	0.72	0.16	0.68	0.11

Note: N=12 at all time points listed except for the 12 hour time point for Day 7 (i.e., (S)-Zopiclone + Digoxin) where N=11. The digoxin concentration for the 12 hour post-dose sample of Subject 188003 was missing due to an inadequate sample volume.

Table 61A: Pharmacokinetic Parameters of Digoxin by Treatment

Parameter (unit)	Statistics	Digoxin Alone	(S)-Zopiclone + Digoxin
C_{max} (ng/mL)	N	12	12
	Mean	2.3	2.1
	SD	0.6	0.6
	%CV	25.4	28.0
	Median	2.3	2.1
	Minimum Maximum	/	/
$AUC_{(0-12)}$ (ng*hr/mL)	N	12	12
	Mean	21.2	21.0
	SD	3.2	2.7
	%CV	15.1	12.7
	Median	20.4	20.5
	Minimum Maximum	/	/
t_{max} (hr)	N	12	12
	Mean	1.2	1.2
	SD	0.4	0.4
	%CV	33.9	32.1
	Median	1.0	1.0
	Minimum Maximum	/	/

SD = standard deviation

Reference: Table 14.2.2, Appendix 16.2.24.

Table 62A: Treatment Comparison of Digoxin Pharmacokinetic Parameters

Parameters	Comparison	Geometric LSmean ¹		Ratio	90% CI	p-value
		(S)-Zopiclone + Digoxin	Digoxin Alone			
C_{max}	Combination/Alone	2.0	2.3	87.7	(80.1, 96.1)	----
$AUC_{(0-12)}$	Combination/Alone	20.8	21.0	99.2	(96.9, 101.6)	----
t_{max} ²	Combination/Alone	1.0	1.0	----	----	0.0684

¹ Geometric LSmean: anti-log of least-squares means derived from the linear model on log-transformed data.

² For t_{max} , the median and the p-value for treatment effect from the ANOVA model were presented.

Comments:

1. The 90% confidence intervals of the ratios for C_{max} (Ratio: 87.7; 90% CI: 80.1, 96.1) and $AUC_{(0-12)}$ (Ratio: 99.2; 90% CI: 96.9, 101.6) were within the 80-125% range demonstrating that the pharmacokinetic profile of digoxin was not affected when digoxin was taken with (S)-zopiclone.

**6.5.4 Individual Study Report- Pharmacodynamic and Pharmacokinetic Interaction Study
Between (S)-Zopiclone and Olanzapine in Healthy Subjects
PROTOCOL NO: 190-018**

Study Introduction

Olanzapine is a marketed antipsychotic agent used predominantly in the treatment of schizophrenia and acts as a selective monoaminergic antagonist. Olanzapine is well absorbed and reaches peak concentrations approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism with approximately 40% of the dose metabolized before reaching the systemic circulation. It displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours and its apparent plasma clearance ranges from 12 to 47 L/hr. Commonly observed adverse events of olanzapine use, with incidences of 5% or greater, are: postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia. Less frequent adverse events associated with olanzapine use include: headache, fever, dry mouth, joint pain, somnolence, agitation, insomnia, nervousness, hostility, anxiety, rhinitis, increased cough, pharyngitis, and amblyopia. Because there is the possibility that the two drugs may be coadministered in this patient population, the current study evaluated the pharmacokinetic and pharmacodynamic interactions of coadministration of single doses of esopiclone and olanzapine.

STUDY OBJECTIVES

To evaluate the pharmacokinetic interactions of single oral doses of 3 mg of esopiclone and 10 mg of olanzapine by comparing monotherapy to combination treatment.

Study Design

This was a single center, inpatient, randomized, parallel, daytime administration, single-dose, single-blind study in healthy male and female subjects. Forty subjects were enrolled.

Schedule: Study participation involved 2 visits: a screening visit and 1 multi-day in-patient visit. Screening (Visit 1) occurred no more than 21 days prior to dosing. Subjects who qualify were admitted on Day -1 of Visit 2. On Day 1 of Visit 2, they were randomized to one of four treatments: placebo, esopiclone, olanzapine or esopiclone in combination with olanzapine. A subject's total study participation was up to 26 days. Visit 2: The in-clinic visits began with admission on the morning before the scheduled dosing. Subjects remained in the Phase I clinic for 4 days post-dosing of placebo, esopiclone monotherapy, olanzapine monotherapy, or esopiclone in combination with olanzapine for safety, pharmacokinetic, and clinical laboratory assessments.

Figure 2A: Study Schematic

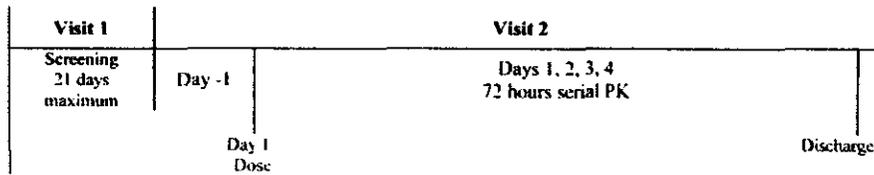


Table 61A: Demographic and Baseline Characteristics

	Placebo (N=10)	Esopiclone (N=10)	Olanzapine (N=10)	Esopiclone + Olanzapine (N=10)
Age				
Mean (SD) years	43.7 (12.0)	39.4 (12.9)	41.8(10.5)	42.1 (11.5)
Min, Max	23, 62	22, 60	25, 57	25, 57
Gender				
Male	3 (30.0%)	2 (20.0%)	4 (40.0%)	3 (30.0%)
Female	7 (70.0%)	8 (80.0%)	6 (60.0%)	7 (70.0%)
Race				
Caucasian	9 (90.0%)	10 (100.0%)	9 (90.0%)	9 (90.0%)
Black	1 (10.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)
Height; mean (SD) cm	172.5 (6.1)	169.8 (5.5)	172.1 (9.4)	170.4 (5.9)
Weight; mean (SD) kg	76.0 (12.8)	67.8 (9.2)	72.2 (15.0)	75.5 (12.5)
BMI; mean (SD) kg/m ²	25.4 (3.6)	23.5 (3.0)	24.2 (3.4)	25.9 (3.5)

TREATMENTS ADMINISTERED

This was a single-blind study. Depending on the randomization, each subject received one of the following:

- Placebo esopiclone 6.0 mg (4 x 1.5 mg)
- Active esopiclone 3.0 mg (2 x 1.5 mg) plus placebo esopiclone 3.0 mg (2 x 1.5 mg).
- Olanzapine 10 mg (1x 10 mg) plus placebo esopiclone 3.0 mg (2 x 1.5 mg).
- Olanzapine 10 mg (1x 10 mg) plus active esopiclone 3.0 mg (2 x 1.5 mg).

The treatment received was either a single dose of placebo, 3 mg esopiclone, 10 mg olanzapine, or 3 mg of esopiclone in combination with 10 mg of olanzapine.

Dose Selection

Olanzapine (Zyprexa ®) is marketed to treat schizophrenia and the target dose of 10 mg has been well tolerated .

Sample Collection and Handling

Plasma samples were drawn from subjects at the following times: Day 1 (Visit 2) pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours (Day 1 [Visit 2]) post-dose. Samples were analyzed for esopiclone and olanzapine.

Bioanalytical Methods-

Studied Period (years): Clinical Conduct August 30, 2000-January 30, 2001

Analysis of plasma samples was conducted from

Theoretical Storage time: s

	Eszopiclone	Olanzapine
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		
Freeze Thaw		

Statistical Analysis

The pharmacokinetic variables included the following for each analyte [esopiclone and olanzapine]:

C_{max}	Maximum observed concentration
t_{max}	Time of occurrence of C_{max} .
C_{last}	The last post-dose quantifiable concentration.
t_{last}	The time of the last post-dose quantifiable concentration.
λ_z	Elimination rate constant
$t_{1/2}$	Terminal phase half-life, calculated as $\ln(2)/\lambda_z$.
$AUC(0-last)$	Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration .
$AUC(0-24)$	Area under the plasma concentration-time curve from time zero to 24 hour post dose.
$AUC(0-\infty)$	Area under the plasma concentration-time curve for the 0-infinity interval.

RESULTS

There were a couple of important protocol errors which resulted in subjects getting the wrong formulation. However, each subject's data were included in the treatment group of the study medication the subject received.

Table 62A: Mean Plasma Concentrations (ng/mL) of Esopiclone Administered Monotherapy and in Combination with Olanzapine

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Time (hr)	Treatment			
	Esopiclone (n=10)		Esopiclone + Olanzapine (n=10)	
	Mean	SD	Mean	SD
Pre-Dose	BLQ	-	BLQ	-
0.5	31.74	16.39	30.65	15.05
1	34.00	5.89	34.00	6.28
1.5	31.85	5.08	31.18	5.95
2	29.73	5.33	29.03	4.49
3	24.11	5.10	23.52	3.55
4	19.27	4.17	19.36	2.87
6	14.42	3.76	14.55	2.09
8	10.60	3.41	10.97	1.94
12	5.89	2.80	6.73	1.37
16	3.74	2.09	4.04	0.79
24	1.51	1.46	1.90	0.51
48	BLQ	-	BLQ	-
72	BLQ	-	BLQ	-

BLQ Below limit of quantification (<1.0 ng/mL)

Table 63A: Mean (SD) Pharmacokinetic Parameters of Esopiclone Administered Monotherapy and in Combination with Olanzapine

Parameter	Treatment	
	Esopiclone (n=10)	Esopiclone + Olanzapine (n=10)
C _{max} (ng/mL)	39.32 -	38.43 -
AUC _(0-last) (ng*hr/mL)	234.47 (-)	242.93 (-)
AUC _(0-∞) (ng*hr/mL)	254.38 (-)	260.90 (-)
t _{max} * (hr)	0.77 (-)	1.00 (-)
t _{1/2} (hr)	6.12 (-)	6.39 (-)

* Values expressed as median (range)

Table 64A: Treatment Comparison of Esopiclone Pharmacokinetic Parameters

Parameter	Treatment	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-last)	Monotherapy	10	227.0	106.02	(89.9, 125.1)	-
	Combination	10	240.7			
C _{max}	Monotherapy	10	38.5	97.08	(81.3, 115.9)	-
	Combination	10	37.4			
t _{1/2}	Monotherapy	10	5.9	106.72	(90.6, 125.6)	-
	Combination	10	6.3			
t _{max} ^c	Monotherapy	10	0.8	-	-	0.4683
	Combination	10	1.0			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was analyzed by the Wilcoxon Rank-Sum test and the median is reported under the Geometric LS Mean.

Table 65A: Mean Plasma Concentrations (ng/mL) of Olanzapine Monotherapy Coadministered with Esopiclone

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ON ORIGINAL

Time (hr)	Treatment			
	Olanzapine (n=10)		Esopiclone + Olanzapine (n=10)	
	Mean	SD	Mean	SD
Pre-Dose	BLQ ^a	-	BLQ ^a	-
0.5	0.21	0.16	0.62 ^a	1.15
1	1.81	0.78	2.69 ^a	2.71
1.5	8.25 ^a	5.26	5.26	4.87
2	12.57	4.67	9.75 ^a	6.66
3	14.86 ^b	3.33	13.54 ^b	4.69
4	16.69 ^a	4.59	14.39 ^a	5.41
6	15.71 ^b	3.85	15.06 ^a	2.75
8	14.20 ^b	3.00	13.92 ^b	2.81
12	11.51 ^a	2.10	11.26 ^a	3.83
16	9.93	2.62	9.61	2.86
24	9.51 ^a	4.03	8.41 ^a	2.64
48	5.13	0.57	5.47	1.32
72	3.45	0.74	3.60	1.39

^a n = 9

^b n = 8

BLQ Below limit of quantification / —

Table 66A: Mean (SD) Pharmacokinetic Parameters of Olanzapine Monotherapy and Coadministered with Esopiclone

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Parameter	Olanzapine (n=10)	Esopiclone + Olanzapine (n=10)
C _{max} (ng/mL)	18.36 (3.24) ^a	17.13 (4.32) ^a
AUC _(0-last) (hr*ng/mL)	542.89 (114.81)	521.37 (124.50)
AUC _(0-∞) (ng*hr/mL)	704.57 (137.38) ^b	645.44 (169.90) ^c
t _{max} ^d (hr)	4.00 (2.00 – 8.00) ^a	6.00 (2.00 – 12.07) ^a
t _{1/2} (hr)	36.78 (9.70)	40.59 (13.79)

^a n = 9; 1 subject excluded (insufficient data around the peak plasma concentration)

^b n = 8; 2 subjects excluded (% extrapolation > 30%)

^c n = 7; 3 subjects excluded (% extrapolation > 30%)

^d Values expressed as median (range)

Table 67A: Treatment Comparison of Olanzapine Pharmacokinetic Parameters

Parameter	Comparison	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-last)	Combination	10	509.3	95.56	(81.1, 112.6)	-
	Monotherapy	10	532.9			
C _{max}	Combination	9	16.6	91.64	(74.7, 112.5)	-
	Monotherapy	9	18.1			
t _{1/2}	Combination	10	38.7	108.34	(87.1, 134.8)	-
	Monotherapy	10	35.8			
t _{max} ^c	Combination	9	6.0	-	-	0.0777
	Monotherapy	9	4.0			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was analyzed by the Wilcoxon Rank-Sum test and the median is reported under the Geometric LS Mean.

Comments:

1. Systemic exposure for esopiclone was not affected by coadministration with olanzapine, as evidenced by the 90% CIs for the ratio of LS means of AUC_(0-last) and C_{max} of the combination compared to monotherapy that were essentially within 80-125%.

Esopiclone was rapidly absorbed following administration of a single 3.0 mg dose both monotherapy and in combination with 10 mg olanzapine, and time to maximum esopiclone plasma concentration was unaffected by coadministration with olanzapine (p = 0.4683). The elimination half-lives of esopiclone following monotherapy and coadministration with olanzapine were also virtually identical.

2. Systemic exposure for Olanzapine was comparable between treatments, as evidenced by the 90% CIs for the ratio of LS means of $AUC_{(0-last)}$ for the combination compared to monotherapy that were included within 80% to 125%. Although the lower bound of the 90% CI for C_{max} was slightly below the 80% limit, the 90% CI included 100%, suggesting that estimates of C_{max} were somewhat variable but similar on average. Olanzapine was gradually absorbed following administration of a single 10 mg dose alone or coadministered with 3.0 mg of esopiclone, and time to maximum olanzapine plasma concentration was unaffected by coadministration with esopiclone ($p = 0.0777$). Estimates of $t_{1/2}$ were also similar on average.

3. There is the possibility that the drug effect of eszopiclone on Olanzapine may be exacerbated due to a diurnal effect which the firm has not investigated since dosing was done at 8:00am.

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**6.5.5 Individual Study Report- .PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION STUDY BETWEEN (S)-ZOPICLONE AND LORAZEPAM
PROTOCOL NO.: 190-019**

Study Introduction

Lorazepam is a marketed anxiolytic used in the treatment of anxiety disorders. Lorazepam is readily absorbed with peak plasma concentrations reached approximately 2 hours following administration. The mean $t_{1/2}$ of lorazepam in human plasma is approximately 12 hours. Commonly observed adverse events include sedation, dizziness, weakness, and unsteadiness. Less frequent adverse events include disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye-function disturbance, and various gastrointestinal symptoms. A previously conducted randomized, placebo-controlled, double blind, single-dose, cross-over study found that the elimination pharmacokinetics of (RS)-zopiclone (7.5 mg) was not affected by diazepam (5 mg) or lorazepam (1 mg) and that the elimination of these benzodiazepine anxiolytics was not altered by (RS)-zopiclone. Furthermore, adverse events experienced after the administration of the active treatments were not significantly different from those experienced after administration of placebo. Because lorazepam is often used in the treatment of anxiety and will therefore potentially be administered concomitantly with (S)-zopiclone, this trial was conducted to study the pharmacodynamics and pharmacokinetics of (S)-zopiclone and lorazepam when administered concomitantly.

Objectives

To evaluate the pharmacodynamic (primary objective) and pharmacokinetic (secondary objective) interactions of single oral doses of 3.0 mg (S)-zopiclone and 2 mg lorazepam in healthy volunteers.

Study Design

This was a single-center, inpatient, randomized, daytime dosing, single-blind, four-arm, parallel, single-dose study in healthy adults. Screening Visit (Visit 1) was completed a maximum of 21 days prior to the first dose. Visit 2: Subjects returned to clinic the day prior to dosing. Subjects were randomly assigned to one of four treatments: placebo, 3 mg (S)-zopiclone, 2 mg lorazepam, or 3 mg (S)-zopiclone and 2 mg lorazepam co-administered. Subjects remained in the Phase I unit for two days following dosing for safety, pharmacodynamic, pharmacokinetic, and clinical laboratory assessments. For each subject, the total time of participation was up to 24 days, including screening.

Dosing was done at 8:00 AM.

TREATMENTS ADMINISTERED

Depending on the randomization, each subject received one of the following:

- Placebo (S)-zopiclone (4 tablets)
- Active (S)-zopiclone (2 x 1.5 mg) and matching placebo (2 tablets).

- Lorazepam (2 x 1.0 mg) and placebo (2 tablets)
- Lorazepam (2 x 1.0 mg) and active (S)-zopiclone (2 x 1.5 mg)

Dose Selection:

In this study, 3.0 mg (S)-zopiclone was utilized, as this is approximately equal to the amount of (S)-zopiclone in the recommended dosage of the marketed racemic product. The 2 mg dose of lorazepam is a commonly marketed dose and is well tolerated.

Table 68A: Subject Demographics

	Placebo N=9 (%)	(S)-Zopiclone N=9 (%)	Lorazepam N=9 (%)	(S)-Zopiclone + Lorazepam N=9 (%)
Age				
Mean (SD) years	40.0 (17.4)	33.4 (13.9)	31.2 (10.3)	31.0 (11.2)
Min, Max	23, 64	20, 62	22, 52	22, 56
Gender				
Male	2 (22.2%)	3 (33.3%)	6 (66.7%)	4 (44.4%)
Female	7 (77.8%)	6 (66.7%)	3 (33.3%)	5 (55.6%)
Race				
Caucasian	6 (66.7%)	7 (77.8%)	9 (100.0%)	7 (77.8%)
Black	2 (22.2%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
Hispanic	1 (11.1%)	1 (11.1%)	0 (0.0%)	1 (11.1%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height; mean (SD) cm	169.9 (11.1)	163.7 (6.7)	173.0 (9.0)	171.8 (11.8)
Weight; mean (SD) kg	70.7 (13.1)	61.2 (11.4)	72.9 (11.7)	72.2 (18.1)
BMI; mean (SD) kg/m ²	24.3 (2.0)	22.8 (3.3)	24.3 (2.9)	24.1 (3.4)

Sample Collection and Handling

Plasma samples were drawn from subjects at the following times: Day 1 (Visit 2) pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours (Day 1 [Visit 2]) post-dose. Samples were analyzed for (S)-zopiclone and lorazepam.

Bioanalytical Methods-Eszopiclone and Lorazepam

Studied Period: August 16-September 24, 2000

The study sample analysis for Eszopiclone and Lorazepam were done between

Theoretical storage time:

	Eszopiclone	Lorazepam
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		
Precision of Standards (%CV)		
Precision of QC Samples (%CV)		
Accuracy of Standards (%)		
Accuracy of QC Samples (%)		
Recovery		
Freeze-Thaw		

Statistical Analysis

The pharmacokinetic parameters were considered secondary outcome variables and included the following for each analyte [(S)-zopiclone and lorazepam]:

- C_{max} Maximum observed concentration.
- t_{max} Time of occurrence of C_{max}.
- C_{last} The last post-dose quantifiable concentration.
- t_{last} The time of the last post-dose quantifiable concentration.

λ_z Elimination rate constant
. $t_{1/2}$ Terminal half-life, calculated as $\ln(2) / \lambda_z$.
AUC(0-last) Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration

AUC(0- ∞) Area under the plasma concentration-time curve for the 0 to infinity interval.

- The effect of lorazepam on the pharmacokinetics of (S)-zopiclone was evaluated by comparing the above mentioned PK parameters following a single oral dose of 3 mg (S)-zopiclone in the absence of lorazepam versus 3 mg (S)-zopiclone and 2 mg lorazepam in combination, with monotherapy as the reference.
- The effect of (S)-zopiclone on the pharmacokinetics of lorazepam was evaluated by comparing the same PK parameters following a single oral dose of 2 mg lorazepam in the absence of (S)-zopiclone versus 3 mg (S)-zopiclone and 2 mg lorazepam in combination, with monotherapy as the reference.

RESULTS

Table 69A: (S)-Zopiclone Plasma Concentration Over Time (Mean \pm SD)

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Time post-dose (hr)	Treatment	
	(S)-Zopiclone (ng/ml)	(S)-Zopiclone + Lorazepam (ng/ml)
Pre-dose	BLQ	BLQ
0.5	25.5 ± 17.4	16.8 ± 9.7
1	35.7 ± 9.5	27.3 ± 9.2
1.5	32.0 ± 6.2	26.4 ± 4.2
2	29.3 ± 4.5	24.9 ± 5.0
3	25.2 ± 4.0	22.9 ± 5.0
4	21.1 ± 3.4	21.3 ± 5.5
6	16.4 ± 3.6	16.2 ± 5.0
8	11.9 ± 2.7	12.2 ± 4.6
12	6.5 ± 1.6	7.1 ± 3.3
16	4.0 ± 1.2	4.2 ± 2.2
24	1.8 ± 0.9	1.9 ± 1.3

NOTE: Number of subjects = 7 at the 0.5- and 1.5-hr time points, and 9 at all other time points (as per Section 9.8.1 and 10.2).

Table 70A: (S)-Zopiclone Pharmacokinetic Parameters

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ON ORIGINAL

Parameter	Treatment	N	Mean ± SD ¹	Combination versus Monotherapy comparison			
				Geometric LS mean ²	Ratio (%) ³	90% CI for Ratio	p-value
C _{max} (ng/ml)	(S)-Zopiclone	9	38.09 ± 9.75	36.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	29.28 ± 7.09	28.5	77.40	[62.3, 96.1]	0.0552
AUC _(0-12hr) (ng*hr/ml)	(S)-Zopiclone	9	248.72 ± 47.61	244.5	-	-	-
	(S)-Zopiclone + Lorazepam	9	236.46 ± 69.53	227.3	92.99	[75.4, 114.7]	0.5542
t _{1/2} (hr)	(S)-Zopiclone	9	5.70 ± 0.98	5.6	-	-	-
	(S)-Zopiclone + Lorazepam	9	5.73 ± 0.91	5.7	100.61	[87.6, 115.5]	0.9397
t _{max} (hr)	(S)-Zopiclone	9	1.00 [0.5, 2.00]	-	-	-	-
	(S)-Zopiclone + Lorazepam	9	1.00 [0.52, 4.03]	-	-	-	0.7115

¹t_{max} provided as Median [Range]

²Geometric LS mean: Geometric least-squares mean. All parameters except t_{max} were log_e transformed. Values of t_{max} were rank-transformed prior to the analysis.

³Ratio (%) of the geometric least-squares means (LS means) for the log_e transformed analysis.

Table 71A: Lorazepam Plasma Concentration Over Time (Mean ± SD)

APPEARS THIS WAY
ON ORIGINAL

Time post-dose (hr)	Treatment	
	Lorazepam (ng/ml)	(S)-Zopiclone + Lorazepam (ng/ml)
Pre-dose	BLQ	BLQ
0.5	10.0 ± 6.3	10.3 ± 4.6
1	22.6 ± 7.8	19.1 ± 8.5
1.5	24.8 ± 11.0	19.9 ± 7.3
2	25.4 ± 12.0	18.7 ± 5.1
3	23.9 ± 9.7	17.8 ± 4.4
4	18.7 ± 3.6	16.6 ± 4.2
6	17.3 ± 4.1	15.3 ± 4.4
8	16.7 ± 7.8	13.8 ± 3.4
12	11.7 ± 3.7	11.6 ± 3.5
16	9.5 ± 3.7	9.3 ± 3.5
24	8.0 ± 3.6	8.0 ± 3.2

Note: Number of subjects = 14 (7 per treatment group) at the 0.5- and 1.5-hr time points, and 18 (9 per treatment group) at all other time points (as per Section 9.8.1 and 10.2).

Table 72A: Lorazepam Pharmacokinetic Parameters

APPEARS THIS WAY
ON ORIGINAL

Parameter	Treatment	N	Mean ± SD ¹	Combination versus Monotherapy comparison			
				Geometric LS mean ²	Ratio (%) ³	90% CI for Ratio	p-value
C _{max} (ng/mL)	Lorazepam	9	27.80 ± 11.56	26.1	-	-	-
	(S)-Zopiclone + Lorazepam	9	21.57 ± 7.54	20.6	78.68	[59.5, 104.0]	0.1532
AUC _(0-last) (ng*hr/mL)	Lorazepam	9	320.85 ± 105.12	304.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	287.51 ± 86.67	275.9	90.48	[69.1, 118.4]	0.5260
t _{1/2} (hr)	Lorazepam	9	15.69 ± 5.33	14.9	-	-	-
	(S)-Zopiclone + Lorazepam	9	19.91 ± 7.87	18.8	125.61	[95.1, 165.9]	0.1720
t _{max} (hr)	Lorazepam	9	1.50	-	-	-	-
	(S)-Zopiclone + Lorazepam	9	1.55	-	-	-	0.5302

¹t_{max} provided as Median [Range]

²Geometric LS mean: Geometric least-squares mean. All parameters except t_{max} were log_e transformed. Values of t_{max} were rank-transformed prior to the analysis.

³Ratio (%) of the geometric least-squares means (LS means) for the log_e transformed analysis.

Comments:

1. The co-administration of (S)-zopiclone (substrate) with lorazepam (interacting drug) decreased the (S)-zopiclone mean C_{max} by 22.6% (90% CI: 62.3, 96.1). There was a 7.01% decrease in AUC.
2. There was no difference in the median t_{max} of (S)-zopiclone when administered as (S)-zopiclone monotherapy or concomitantly with lorazepam (median t_{max} = 1 hour). The mean t_{1/2} for (S)-zopiclone was not affected by co-administration of lorazepam (mean t_{1/2} = 5.70 hours and 5.73 hours, respectively).
3. The co-administration of lorazepam (substrate) with (S)-zopiclone (interacting drug) decreased the lorazepam mean C_{max} by 21.3% (90% CI: 59.5, 104.0) and the lorazepam mean AUC(0-last) by 9.5% (90% CI: 69.1, 118.4).
4. The median t_{max} for lorazepam was not affected by co-administration of (S)-zopiclone (median t_{max} = 1.50 hours and 1.55 hours, respectively). The mean t_{1/2} for lorazepam was slightly greater when (S)-zopiclone was co-administered (mean t_{1/2} = 15.69 hours-alone and 19.91 hours -combination, respectively); however, this difference was not statistically significant.
5. There is the possibility that the drug interaction may be exacerbated due to a diurnal effect which the firm has not been investigated since dosing was done at 8:00am.

6.5.6 Individual Study Report PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION STUDY BETWEEN (S)-ZOPICLONE AND PAROXETINE IN HEALTHY SUBJECTS-PROTOCOL NO: 190-020

Study Introduction

Paroxetine is a widely prescribed antidepressant that acts as a selective serotonin reuptake inhibitor. In studies where healthy subjects received daily doses of paroxetine for thirty days, steady state paroxetine concentrations were achieved by approximately 10 days. At steady state, the mean half life of paroxetine is 21 hours. Paroxetine is extensively metabolized by cytochrome P-450 (CYP) 2D6 after oral administration. Commonly observed adverse events following paroxetine use are asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, sweating, decreased libido, ejaculatory disturbance, and impotence. No new adverse events are expected with the combined dosage of esopiclone and paroxetine. Because paroxetine is a CNS-active drug, a commonly used antidepressant and is extensively metabolized by CYP 2D6, this trial was conducted to study the single dose effect primarily on the pharmacodynamics and secondarily on the pharmacokinetics of esopiclone and paroxetine when administered concomitantly. No pharmacokinetic interactions were expected, as esopiclone is not metabolized by or an inhibitor of CYP 2D6. In addition, because the adverse event of somnolence is commonly observed following paroxetine use, this trial was conducted to study this parameter.

Objectives

The primary objective was to evaluate the pharmacodynamic interaction of single oral doses of 3 mg esopiclone and 20 mg paroxetine in healthy volunteers. The secondary objective was to evaluate the pharmacokinetic interactions of single oral doses of 3 mg esopiclone and 20 mg paroxetine in healthy volunteers.

Study Design

This was a single-center, inpatient, randomized, four-arm parallel, daytime administration, single-dose, single-blind study in normal healthy male and female volunteers. Forty subjects were enrolled. Dropouts were not to be replaced. Study participation involved 2 visits: a screening visit and one multi-day inpatient visit. Screening (Visit 1) occurred no more than 21 days prior to the inpatient confinement for Visit 2 dosing. Subjects who qualified were admitted on Day -1 of Visit 2 and randomized to one of four treatments: placebo, esopiclone, paroxetine or esopiclone and paroxetine combination therapy. The inpatient visit (Visit 2) began with clinic admission no later than 10:00 on the morning before the scheduled dosing. The subjects remained in the Phase I clinic for 2 days post-dosing for safety, pharmacodynamic, pharmacokinetic, and clinical laboratory assessments. A subject's total study participation was up to 24 days, from screening to study termination.

Amendment to Study Design

Amendment 1 was created to allow up to 40 subjects (an additional 16 subjects) to be dosed. The purpose of the additional subjects was to increase the power. The additional 16 subjects

were to be dosed at the same site as the original 24, but occurred several months after the initial cohort was done. The cohort and cohort by treatment effect were assessed in addition to performing the analysis planned in the protocol. Analysis of the cohort and cohort by treatment effects were performed.

TREATMENTS ADMINISTERED

Depending on the randomization, each subject received one of the following:

- Placebo esopiclone (4 tablets)
- Active esopiclone (2 x 1.5 mg) and matching placebo (2 tablets).
- Paroxetine (2 x 10 mg) and placebo (2 tablets)
- Paroxetine (2 x 10 mg) and active esopiclone (2 x 1.5 mg)

Dose Selection

In this study, 3 mg esopiclone was utilized, as this is approximately equal to the amount of esopiclone in the recommended dosage of the marketed racemic product. Paroxetine (Paxil[®]) is marketed for depression and 20 mg has been well tolerated.

Based on the clinical condition being studied (i.e., insomnia), esopiclone is being developed as a once-a-day formulation. Study medication was administered at approximately 08:00 AM of the dosing day.

Subject Demographics

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	Placebo (N=10)	Esopiclone (N=10)	Paroxetine (N=10)	Esopiclone + Paroxetine (N=10)
Age				
Mean (SD) years	32.5 (9.3)	36.7 (11.9)	32.9 (8.3)	30.8 (9.8)
Min, Max	21, 51	21, 52	21, 47	23, 55
Gender				
Male	6 (60.0%)	7 (70.0%)	7 (70.0%)	7 (70.0%)
Female	4 (40.0%)	3 (30.0%)	3 (30.0%)	3 (30.0%)
Race				
Caucasian	6 (60.0%)	10 (100.0%)	8 (80.0%)	8 (80.0%)
Black	3 (30.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
Asian	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
Hispanic	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height; mean (SD) cm	174.8 (9.2)	174.4 (8.9)	172.5 (10.4)	171.3 (13.1)
Weight; mean (SD) kg	76.4 (14.9)	77.5 (9.9)	77.4 (10.3)	72.3 (16.3)
BMI; mean (SD) kg/m ²	24.8 (3.1)	25.5 (2.6)	26.0 (2.4)	24.2 (2.2)
Phenotype				
Extensive Metabolizer	10 (100.0%)	10 (100.0%)	9 (90.0%)	9 (90.0%)
Poor Metabolizer	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)

Sample Collection and Handling

Plasma samples were drawn from subjects at the following times: Day 1 (Visit 2) pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours (Day 1 [Visit 2]) post-dose. Samples were analyzed for esopiclone and paroxetine.

Bioanalytical Methods-Eszopiclone

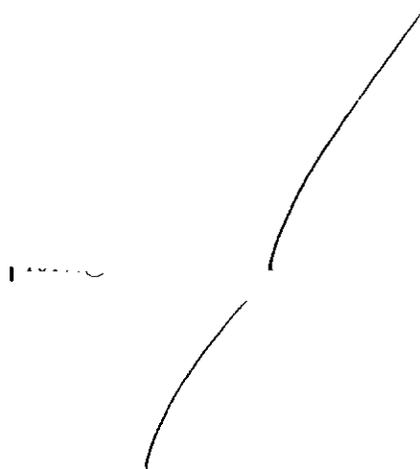
Studied Period: September 1, 2000-December 17, 2000

The study sample analysis for Eszopiclone and Paroxetine were done between _____

Theoretical storage time: _____

	Eszopiclone	Paroxetine
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ		
Linearity (Standard curve samples)		
Quality Control (QC) Samples		

Precision of Standards (%CV)
Precision of QC Samples (%CV)
Accuracy of Standards (%)
Accuracy of QC Samples (%)
Recovery
Freeze-Thaw



Statistics

The pharmacokinetic parameters were considered secondary outcome variables and included the following for each analyte [esopiclone and paroxetine]:

C _{max}	Maximum observed concentration.
t _{max}	Time of occurrence of C _{max} .
C _{last}	The last post-dose quantifiable concentration.
t _{last}	The time of the last post-dose quantifiable concentration.
λ _z	Elimination rate constant .
t _{1/2}	Terminal phase half-life, calculated as ln(2)/ λ _z .
AUC(0-last)	Area under the plasma concentration-time curve from time zero to the time of the last post-dose quantifiable plasma concentration
AUC(0-∞)	Area under the plasma concentration-time curve for the 0 to infinity interval.

Results

Table 73A: Esopiclone Plasma Concentration Over Time (Mean ± SD)

Time (hr)	Treatment	
	Esopiclone (ng/mL)	Esopiclone + Paroxetine (ng/mL)
Pre-Dose	BLQ	BLQ
0.5	15.37 ± 10.56	23.91 ± 15.41
1	25.92 ± 4.09	27.53 ± 7.38
1.5	25.85 ± 4.32	26.78 ± 7.46
2	25.02 ± 3.01	27.22 ± 7.60
3	21.51 ± 2.93	22.89 ± 4.59
4	19.40 ± 2.65	20.39 ± 3.93
6	14.45 ± 2.82	14.84 ± 3.36
8	10.93 ± 3.07	11.64 ± 2.95
12	6.49 ± 2.49	7.06 ± 2.24
16	4.11 ± 2.15	4.48 ± 1.74
24	1.81 ± 1.71	2.32 ± 1.44

BLQ: Below limit of quantification

Table 74A: Esopiclone Pharmacokinetic Parameters (Mean ± SD)

Parameter	Monotherapy (n=10)	Combination (n=10)
C _{max} (ng/mL)	27.91 ± 3.90	31.87 ± 8.74
AUC _(0-last) (hr*ng/mL)	220.73 ± 53.08	241.20 ± 53.53
AUC _(0-∞) (hr*ng/mL)	243.25 ± 73.87	270.18 ± 71.29
t _{max} ^a (hr)	1.25 -	1.25 -
t _{1/2} (hr)	6.18 ± 1.69	7.20 ± 2.14

^a t_{max} is presented as Median (Range)

Table 75A: Treatment Comparison of Esopiclone Pharmacokinetic Parameters

Parameter	Treatment	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-12h)	Monotherapy	10	215.1	109.25	(90.3, 132.2)	0.4306
	Combination	10	235.0			
C _{max}	Monotherapy	10	27.7	111.63	(94.8, 131.4)	0.2582
	Combination	10	30.9			
t _{1/2}	Monotherapy	10	6.0	116.53	(95.7, 141.8)	0.1939
	Combination	10	7.0			
t _{max} ^c	Monotherapy	10	1.3 ^d	-	-	1.0000 ^e
	Combination	10	1.3 ^d			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was rank-transformed

^d Median

^e p-value for the testing the difference in the medians.

76A: Paroxetine Plasma Concentration Over Time (Mean ± SD)

Time (hr)	Treatment	
	Paroxetine (ng/mL)	Paroxetine + Esopiclone (ng/mL)
Pre-Dose	BLQ	BLQ
0.5	BLQ	BLQ
1	BLQ	BLQ
1.5	1.81 ± 1.46	1.12 ± 1.33
2	3.14 ± 3.24	1.53 ± 1.82
3	6.23 ± 5.12	5.16 ± 4.32
4	8.13 ± 6.10	6.75 ± 4.98
6	8.63 ± 6.74	7.40 ± 6.71
8	7.66 ± 6.48	6.97 ± 7.04
12	5.81 ± 6.03	5.38 ± 7.03
16	4.91 ± 6.11	3.96 ± 4.94
24	3.61 ± 5.75	4.32 ± 6.18

BLQ: Below limit of quantification

Table 77A: Paroxetine Pharmacokinetic Parameters (Mean ± SD)

Parameter	Monotherapy ^a	Combination ^a
C_{max} (ng/mL)	9.34 ± 7.07	9.24 ± 6.71 ^b
$AUC_{(0-last)}$ (hr*ng/mL)	128.38 ± 130.57	126.95 ± 128.38 ^b
t_{max} ^c (hr)	4.00 —	4.00 —
$t_{1/2}$ (hr)	12.04 ± 7.51 ^d	11.37 ± 4.91 ^e

^a n = 10 unless otherwise noted

^b n = 9; 1 subject excluded (< 4 measurable plasma concentrations)

^c t_{max} is presented as Median (Range)

^d n = 8; 2 subjects excluded (unable to characterize terminal phase)

^e n = 4; 6 subjects excluded (unable to characterize terminal phase)

Table 78A: Treatment Comparison of Paroxetine Pharmacokinetic Parameters

Parameter	Comparison	N	Geometric LS mean ^a	Combination versus Monotherapy Comparison		
				Ratio (%) ^b	90% CI	p-value
AUC _(0-24h)	Monotherapy	10	71.5	96.45	(34.0, 273.9)	0.9527
	Combination	9	69.0			
C _{max}	Monotherapy	10	7.0	101.62	(52.5, 196.5)	0.9666
	Combination	9	7.1			
t _{1/2}	Monotherapy	8	10.5	99.43	(56.5, 175.0)	0.9858
	Combination	4	10.5			
t _{max} ^c	Monotherapy	10	4.0 ^d	-	-	0.3219 ^e
	Combination	9	4.0 ^d			

^a Geometric LS mean: Geometric least-squares mean, anti-log of least squares means derived from the linear model.

^b Ratio (%) of the geometric means (LS means) for the log_e transformed analysis.

^c t_{max} was rank-transformed

^d Median

^e p-value for the testing the difference in the medians.

Comments:

1. There was a 9% and an 11% increase in AUC and C_{max} respectively when esopiclone was the substrate and paroxetine the interacting drug. The 90% CI were (90.3-132.2) and (94.8-131.4) however this was due to the size of N=10 and a parallel study design so the result was not considered to be statistically meaningful.

2. There was a 5% decrease in AUC when paroxetine was the substrate and esopiclone the interacting drug. The 90% CI were (34.0-273.9) which was due to the size of N=10 and a parallel study design so the result was not considered to be statistically meaningful. The reason for the large variability for the paroxetine results is that there exists two populations of metabolizers for this 2D6 metabolized substrate.

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6.5.7 –Meta-Analysis Protocol # 190-000-K01

A Meta-Analysis of the Relationship Among Selected Demographic Variables and Exposure to Esopiclone in Healthy Subjects

6 OBJECTIVE

The primary objective of these analyses was to evaluate the effect of age, race, gender, and weight on exposure (C_{max} and AUC) to esopiclone following single and multiple dose administration.

7 INVESTIGATIONAL PLAN

7.1 DATA SOURCES AND ASSEMBLY

The pharmacokinetic data were integrated from 11 Phase I safety and pharmacokinetic studies in healthy subjects. Ten of the studies were carried out in subjects from 18 to 64 years of age and one study (Sepracor (SEPR) Study No. 190-005) included only elderly subjects (≥ 65 years). A summary of all the pharmacokinetic studies included in the pharmacokinetic demographic meta-analysis is provided in Table 7.1-1. The detailed information for all the study designs can be found in individual study reports. All data processing was performed using SAS® Software, Version 6.12.

The pharmacokinetic meta-demographic analysis included only healthy fasted subjects who had taken esopiclone alone (tablets or solution) to investigate potential demographic effects on the esopiclone pharmacokinetics.

Esopiclone pharmacokinetic parameters of maximum concentration (C_{max}) and area under the concentration-time curve (AUC) provided an assessment of esopiclone exposure. At steady-state, the AUC over the dosing interval $AUC_{(0-\infty)}$ was utilized. After single dose, $AUC_{(0-\infty)}$ was chosen for analysis because it is the most appropriate measure used to estimate clearance and, in theory, is equal to $AUC_{(0-\tau)}$ at steady-state. In addition, all subjects had measures of $AUC_{(0-\tau)}$.

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Results for Gender AUC(0-tau)

9.2.2.2 Esopiclone AUC_(0-τ) at Steady State

Descriptive statistics for the steady-state esopiclone AUC_(0-τ) by gender, age and race are presented in Tables 9.2.2.2-1 to 9.2.2.2-3. Individual esopiclone AUC_(0-τ) values distributed by gender, age, race, and body weight are graphically presented in Figures 9.2.2.2-1 to 9.2.2.2-4, respectively.

Table 9.2.2.2-1 Dose-Normalized* Steady State Esopiclone AUC_(0-τ) by Gender

Parameter	Statistic	Gender	
		Male	Female
AUC _(0-τ) ng•hr/mL per mg	N	60	26
	Mean	73.8	92.2
	SD	22.1	18.1
	Median	71.6	88.1
	Min	/	/
	Max	/	/

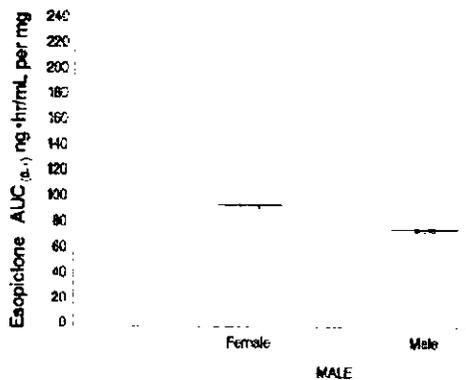
* AUC_(0-τ) values were dose normalized to 1 mg of esopiclone

Note: A total of 86 AUC_(0-τ) values from 86 subjects are summarized

Reference: Table 11.2 and Appendix 12.1.2

As shown in Table 9.2.2.2-1 and Figure 9.2.2.2-1, the mean esopiclone AUC_(0-τ) in females was approximately 25% higher than in males at steady state but, the range of values overlapped between the two gender groups.

Figure 9.2.2.2-1 Dose-Normalized* Steady State Mean and Individual Esopiclone AUC_(0-τ) Values By Gender



* AUC values were dose normalized to 1 mg esopiclone
Solid line indicates the group mean.

6.5.8 Dissolution Data for Pivotal Biobatches F0468003-2 mg and F0548002-3 mg.

Dissolution Profiles for 2.0 mg Drug Product Batch F0468003

Batch F0468003/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	78.5	86.2	92.7	96.3	99.0
RSD (%)	8.8	5.5	3.5	3.0	2.6

Dissolution Profiles for 3.0 mg Drug Product Batch F0548002

Batch F0548002/ Tablet No.	% Dissolved in Stated Time (Minutes)				
	5	10	20	30	45
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
High (%)					
Low (%)					
Average (%)	76.7	84.1	89.8	92.6	95.2
RSD (%)	10.0	6.6	4.4	3.5	2.8

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Raman Baweja
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BIOPHARMACEUTICS

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/s/

Thomas Oliver
10/1/03 09:29:52 AM