CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Zolpidem Tartrate
NDA:	21-997
SUBMISSION DATE	05/14/2008
PRODUCT (Brand Name):	——— b(4)
DOSAGE FORM:	Sublingual Tablet
DOSAGE STRENGTHS:	5 and 10 mg
INDICATION:	Short-term treatment of insomnia characterized by difficulties with sleep initiation
NDA TYPE:	505 (b)(2)
SPONSOR:	Orexo Pharma Inc.
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Veneeta Tandon, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY 2

A. RECOMMENDATION 3
B. PHASE IV COMMITMENTS 3
C. PRESUBMISSION REGULATORY ACTIVITY RELATED TO SUBMISSION 3
D. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS 4

II. QUESTION BASED REVIEW 7

A. GENERAL CLINICAL PHARMACOLOGY 8
B. INTRINSIC FACTORS 10
C. EXTRINSIC FACTORS 10
D. GENERAL BIOPHARMACEUTICS 10
E. ANALYTICAL 21

III. LABELING RECOMMENDATIONS 23

IV. APPENDIX **56**

A INDIVIDUAL STUDY SYNOPSIS 56

OX22-001: An open randomized three-period crossover single-centre study to evaluate the pharmacokinetic profile of sublingual zolpidem 5 mg and 10 mg, and of oral zolpidem (Stilnoct®) 10 mg *56*

OX22-004: An open randomized two-period crossover study to assess the bioavailability of sublingual zolpidem for the treatment of short-term insomnia *61*

OX22-005: An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for the treatment of short-term insomnia *65*

OX22-008: An open randomized two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia *71*

OX22-006: A double-blind, randomized, two-period crossover study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia. *76*

B OCP FILING MEMO 84

I. EXECUTIVE SUMMARY

Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class for the short term treatment of insomnia characterized by difficulties with sleep initiation. Oral tablets of zolpidem tartrate are currently marketed **under trade name of Ambien®.** ——— **is a** sublingual tablet formulation of zolpidem tartrate. The proposed indication for this is also the short term treatment of insomnia. The current 505(b)(2) NDA seeks approval of ——— **5 mg, and 10 mg a sublingual tablet form of zolpidem tartrate.** ——— was designed to show bioequivalence between this new sublingual dosage form of zolpidem tartrate and reference Ambien® tablets.

b(4)

This NDA comprises of the following 2 single-dose pharmacokinetic (PK)/bioequivalence (BE) bridging studies in healthy adult subjects, 18- 40 years of age: Study OX22-005, Formulation II (10 mg OX22) versus 10 mg Ambien® and Study OX22-008, Formulation **II versus the Final Commercial Product (10 mg** ——— **).**

b(4)

Formulation II was found to be bioequivalent to the RLD Ambien®. However, Formulation II is not the to-be-marketed or commercial formulation. Therefore the Sponsor has also conducted a bridging BE study between Formulation II and the commercial formulation (Study OX22-008). Formulation II was bioequivalent to the commercial formulation, thereby establishing the link between the commercial formulation and the reference Ambien®.

Food effect on pharmacokinetic profile of zolpidem after sublingual administration was evaluated using formulation II in study OX22-005. A statistically significant lower bioavailability was observed for sublingual zolpidem with meal compared to sublingual zolpidem under fasting conditions.

In addition to this, the submission also contained 2 pilot studies, evaluating the BE between two formulations (formulation I and formulation II) of sublingual dosage form (study OX22-004) and a BE study comparing formulation I to Stilnoct®, a European product.

This NDA also contained a single dose pharmacodynamic study (study OX22-006) and an open label study OX22-007 in patients with chronic insomnia that evaluated local tolerance after daily administration of 10 mg zolpidem sublingual tablets for 60 days.

Hypnotic effects of sublingual zolpidem (formulation II) study OX22-006 were compared with the reference Ambien® on sleep initiation, sleep continuity (maintenance), sleep **architecture and profile parameters as well as on the patients' subjective assessments and the** next day residual effects.

A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 21-997. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view pending results of the DSI inspection for the bioequivalence and formulation bridging studies.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review should be conveyed to the sponsor.

Clinical Pharmacology briefing was held on 02/10/09 and the attendees were Drs. Ramana Uppoor, Veneeta Tandon, Ronald Farkas, Sripal Mada and Hristina Dimova.

B. Phase IV Commitments

None.

C. Presubmission Regulatory Activity Related to Submission

Initial NDA was submitted on 01/12/2006. Following NDA submission on 01/12/2006, the FDA issued RTF letter on 03/13/2006. The Sponsor submitted the European Pharmacopoeia for reference, and did not use the US approved reference drug product Ambien® to establish bioequivalence (instead studies were done using Stilnoct®, Zoplidem oral formulation available in Europe). For the sublingual formulation there was lack of safety data on local (sublingual) irritation after long term use, and other safety concerns raised by the Controlled Substance Staff (CSS). A teleconference with the Sponsor on 05/01/2006 addressed NDA deficiencies and the FDA advised the Sponsor to proceed with further studies and incorporate suggestions through IND 69,200 to support the NDA 505 (b)(2) application.

b(4)

D. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Bioequivalence: Sponsor has conducted a BE study comparing Formulation II with the reference Ambien® (Study OX22-005). Formulation II was found to be bioequivalent to the RLD Ambien®. Time to reach maximum plasma concentration, tmax did not differ significantly from the reference Ambien®. However, Formulation II is not the to-be-marketed or commercial formulation. Therefore the Sponsor has also conducted a bridging BE study between Formulation II and the commercial formulation (Study OX22-008). Formulation II was bioequivalent to the commercial formulation, thereby establishing the link between the commercial formulation and the reference Ambien®.

The overall conclusions from the two BE studies are summarized below:

Study OX22-005: This study was conducted to establish bioequivalence between formulation II and the reference Ambien®.

Following table indicates primary pharmacokinetic parameters ratios and 90% confidence intervals levels based on sponsor's analysis.

Table 1: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Sponsor's Analysis)

b(4)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
FASTING/AMBIEN® FASTING	AUC_{0-t}	108.0	99.35	117.5
	$AUC_{0-\infty}$	107.6	98.6	117.5
	C_{max}	106.0	105.0	120.1

Reviewer's re-analysis of the data showed similar 90% confidence interval (CI), with the exception of lower boundary of 90% CI for Cmax; being 91.7 in the reviewer analysis and 104.9 in the sponsor analysis. However 90% CIs were within acceptable limits as shown in the table below.

Table 2: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Reviewer's Analysis)

b(4)

TREATMENT COMPARISONS	PARAMETER	RATIO	LOWER 90% CI	UPPER 90% CI
FASTING/AMBIEN® FASTING	$AUC_{0-\infty}$	107.6	98.6	117.5
	C_{MAX}	104.9	91.7	120.1

b(4) **The results showed that,** **was bioequivalent to reference Ambien® under fasting conditions. The median tmax's were** 82 (range 30-180) minutes for formulation II and 90 (range: 30-180) minutes for Ambien® and these differences were not statistically significantly different.

Study OX22-008: This study was conducted to establish bridging link between formulation II and to-be-marketed formulation, final commercial product (FCP). The 90% **CIs based on sponsor's analysis are shown in the following table.**

Table 3: Treatment Comparisons for FCP versus Formulation II

		90% Confidence Interval	
Pharmacokinetic variable	**Point estimate**	**Lower limit**	**Upper limit**
AUC_{0-t} (hr*ng/mL)[1)]	1.10	1.02	1.19
$AUC_{0-\infty}$ (hr*ng/mL)[1)]	1.12	1.01	1.23
C_{max} (ng/mL)[2)]	1.08	0.99	1.18

Reviewer's re-analysis of the data showed differences in the point estimate ratios and 90% confidence interval (CI) levels for lower boundary and upper boundary. However 90% CIs were within acceptable limits as shown in the table below.

Table 4: Pharmacokinetic Parameter Ratios of Point Estimates and 90% **Confidence Intervals (Reviewer's Analysis)**

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
FCP/ Formulation II	$AUC_{0-\infty}$	1.12	0.8142	0.9863
	C_{max}	1.08	0.8453	1.0144

The results showed that, formulation II was bioequivalent to final commercial product under fasting conditions. The median tmax's **were 120 (range: 60-240) minutes for** formulation II and 120 (range: 20-180) minutes for FCP.

Food Effect: Food effect on pharmacokinetic profile of zolpidem after sublingual
b(4) administration was evaluated using formulation II in study OX22-005, formulation II was found to be bioequivalent to the commercial formulation. The 90% CI for the effect of food on **the** **is shown in the following table.**

Table 5: Pharmacokinetic Parameter Ratios of Point Estimates and 90% **Confidence Intervals (Reviewer's Analysis)**

TREATMENT COMPARISONS	PARAMETER	RATIO	LOWER 90% CI	UPPER 90% CI

b(4)

FED/ FASTING	$AUC_{0-\infty}$	0.802	0.735	1.175
	C_{MAX}	0.688	0.601	0.876

The results showed that the AUC and Cmax were decreased by 20 and 30% respectively under fed conditions compared to fasted conditions. Median tmax for with meal was prolonged by 28% from 82 to 105 minutes. Therefore for earlier sleep onset TRADENAME should not be administered with or immediately after a meal. b(4)

Dose proportionality: Dose-proportionality of the zolpidem plasma concentrations resulting from the administration of the sublingual tablet 5 and 10 mg was determined in Study OX22-001 (using Formulation I). The results indicated that the sublingual tablet formulation was dose-proportional with respect to zolpidem PK parameters. Dose proportionality was not assessed with formulation II or FCP. However, formulation I was bioequivalent to formulation II, however the tmax of formulation I was approximately 45% lower than formulation II.

The dose proportionality between the 5 and10 mg, supports the use of 5 mg in the elderly populations.

Pharmacodynamics: Sponsor has conducted a single dose, double-blind, randomized, two-period crossover study to evaluate hypnotic effects of sublingual zolpidem for treatment of insomnia in comparison with Ambien®.

b(4) Compared to Ambien®, significantly shortened the primary end points, sleep initiation (LPS) and two secondary sleep initiation endpoints (SOL and ST1L). However, for non-inferiority limit was not achieved for two other endpoints of the primary objectives (wake after sleep onset, WASO and total sleep time, TST),.

Secondary pharmacodynamic endpoints were also assessed by next day subjective assessment of residual effects include, Visual Analogue Scale (VAS) for alertness, contentedness and calmness, Digit Symbol Substitution Test (DSST) for attention and b(4) concentration, Leeds psychomotor tests (MCRT and CFFT) for attention abilities and vigilance. Results of the next day residual effects indicated that there were no differences between and Ambien®.

Ambien® has been shown to decrease sleep latency for up to 35 days in controlled clinical trials, according to the Ambien® label. The Study OX22-006 is a single-dose study evaluating pharmacodynamic (PSG) parameters and as such the design of the study is not adequate in assessing the pharmacodynamic effects. The adequacy of this single dose b(4) study in assessing hypnotic effect of sublingual tablets will also be assessed by the medical reviewer. The adequacy of the labeling recommendations of this study should also be considered by the medical officer.

II. QUESTION BASED REVIEW

General Attributes

Drug/Drug Product Information:

Dosage Form/Strengths: [redacted] **is a sub**lingual tablet formulation of zolpidem tartrate. The commercial formulation is shown in the following table. b(4)

Table 6: Final Commercial Product (FCP) - Composition of Zolpidem tartrate sublingual tablets 5 and 10 mg

Components	Each 5 mg tablet contains (mg)	Each 10 mg tablet contains (mg)	Function	Reference to quality standard
Zolpidem tartrate, micronized	5.00	10.0	Drug substance	Ph. Eur.
Mannitol				USP, Ph. Eur.
Silicified microcrystalline cellulose[3]				USP, Ph. Eur.
Silicon dioxide, colloidal				USP, Ph. Eur. b(4)
Croscarmellose sodium				USP, Ph. Eur.
Saccharin sodium				USP, Ph. Eur.
Magnesium stearate				USP, Ph. Eur.
Tablet weight	**120 mg**	**130 mg**		

Indication: **(zolpidem tartrate) is indicate**d for indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. b(4)

What is the proposed mechanism (s) of action?

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. Zolpidem *in vitro* binds the (BZ_1) receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. The (BZ_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum

molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (BZ_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (Stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

A. General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical trials conducted by the sponsor to support the approval [redacted] are summarized in the following table: b(4)

Table 7: Clinical trials in support of the [redacted] b(4)

Trial ID	Study Type	Study Title	No. of Subjects Enrolled	Formulation of [redacted]
OX22-005	Bioequivalence trial in healthy adults	An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for the treatment of short-term insomnia	Healthy, adult (18–40 years of age) male and female volunteers (n=18)	Formulation II (10 mg [redacted] versus 10 mg Ambien®
OX22-008	Formulation Bridging Study	An open randomized, two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia.	Healthy volunteers, males or females, between 18 and 45 years of age, fasting (n=19) 7 males 12 females	Formulation II versus the Final Commercial Product (10 mg [redacted])
OX22-006	Pharmacodyna-mic Study	A double-blind, randomized, two period cross-over study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia	Male and female patients between 18 and 65 years (n=73) 31 males 42 females	Formulation II(10 mg sublingual tablets [redacted])

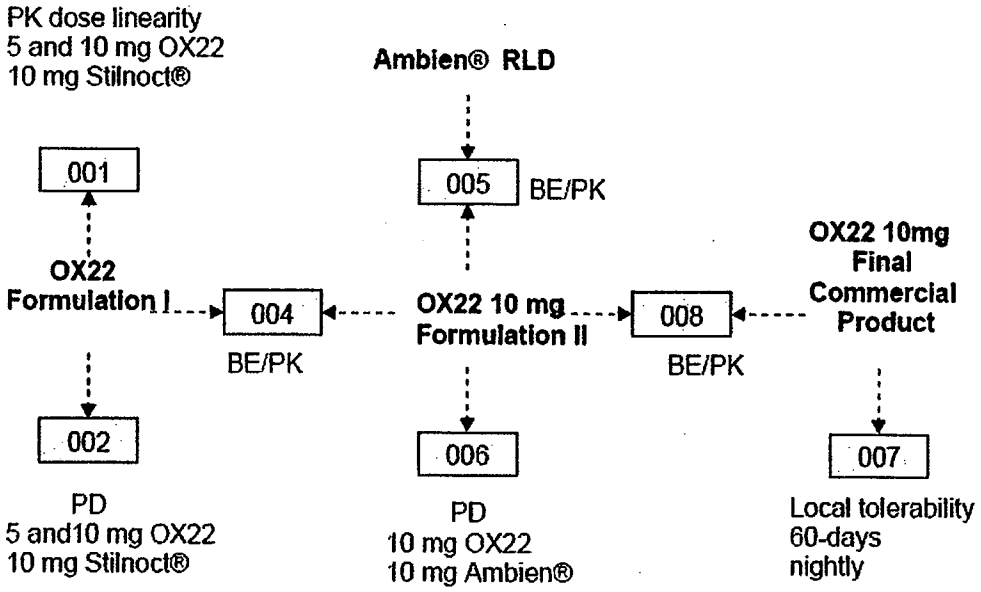
OX22-001	Bioequivalence study with Stilnoct® (EMEA approved zolpidem oral tablet) as a reference	An open randomized, three-period crossover, single-centre study to evaluate the pharmacokinetic profile of sublingual zolpidem 5 mg and 10 mg, and of oral zolpidem (Stilnoct®) 10 mg	Healthy, adult **(18–40 years of** age) male volunteers (n=18)	Formulation I (5 mg and 10 mg sublingual tablets,) b(4)
OX22-004	Formulation Bridging Study	An open randomized, two-period crossover, study to assess the bioavailability of sublingual zolpidem for the treatment of short term insomnia	Healthy, adult **(18–40 years of** age) male volunteers (n=12)	Formulation II (10 mg sublingual tablets) Formulation I (10 mg sublingual tablets)
OX22-002	Hypnotic efficacy and safety Study	An open randomized, three-period crossover, single-centre study to evaluate the hypnotic efficacy and safety of sublingual zolpidem 5 mg and 10 mg compared to oral zolpidem (Stilnoct®) 10 mg in healthy volunteers	Healthy male or female volunteer subjects. 18-40 years 4 males 17 females	Formulation I (5 mg and 10 mg sublingual tablets)
OX22-007	Local tolerance and safety Study	An open labeled clinical trial evaluating the local tolerance and safety of sublingual zolpidem in insomnia patients	60 patients planned/ 60 enrolled/ 53 per protocol/ 60 safety analyses 10 mg OX22	Final Commercial Product (10 mg sublingual tablets)

Study OX22-005 provides bioequivalence data re**garding the sublingual tablet** in reference to Ambien®. Study OX22-008 provides formulation bridging data between formulation II and final commercial formulation. b(4)

Following schematic diagram represents bridging studies using different formulations **during the clinical development** .

Schematic diagrams representing bridging studies

Figure 1: OX22 Clinical Development



Stilnoct® Oral zolpidem, Sanofi-Aventis, EU

B. Intrinsic Factors

The effects of various intrinsic factors (e.g., hepatic, renal) were provided in the original NDA for each drug. Please see Clinical Pharmacology reviews for Ambien® (zolpidem tartrate) tablets NDA 19-908.

C. Extrinsic Factors

Is there any drug-drug interaction between zolpidem and other drugs?

No drug-drug interaction studies were conducted with ——— [redacted]. Drug-drug interaction information related to zolpidem tartrate is provided in the original NDA for each drug. Please see Clinical Pharmacology reviews for Ambien® (zolpidem tartrate) tablets NDA 19-908. b(4)

D. General Biopharmaceutics

What is the formulation of ——— sublinigual tablet b(4)

The sponsor has developed a sublingual tablet formulation containing the active ingredient zolpidem tartrate at two dosage strengths, 5 and 10 mg. Dosage strengths 5 and 10 mg are

compositionally proportional. The composition of commercial zolpidem tartrate sublingual tablets 5 and 10 mg are given on page 9 of the review.

Three different formulations were used during the clinical development of including formulation I, formulation II and final commercial formulation. Formulation II was used in the BE study and a second bridging study was conducted between formulation II and final commercial product. Formulation I was used in pilot BE studies. Following table represents compositions of sublingual zolpidem tablet formulations. Following table compares the ingredients of these formulations. b(4)

Table 8: Formulations of Zolpidem tartrate sublingual tablets used in clinical development program

Components	**Function**	**Formulation I (mg)**	**Formulation II (mg)**	**Final Commercial Product (mg)**
Zolpidem tartrate,	Drug substance	5.00/10.0		
Zolpidem tartrate,	Drug substance	-	10.0	10.0
Mannitol				
Silicon dioxide, colloidal				
Silicified microcrystalline cellulose				
Croscarmellose sodium				
Saccharin sodium				
Magnesium stearate				
Total weight		**80.0 mg**	**105 mg**	**130 mg**
Formulation(s) used for clinical programs				
		OX22-001		
		OX22-002		
		OX22-004[6]	OX22-004	
			OX22-005	
			OX22-006	
				OX22-007
			OX22-008	OX22-008

b(4)

b(4)

Is ——— bioequivalent to Ambien® tablets in healthy subjects?

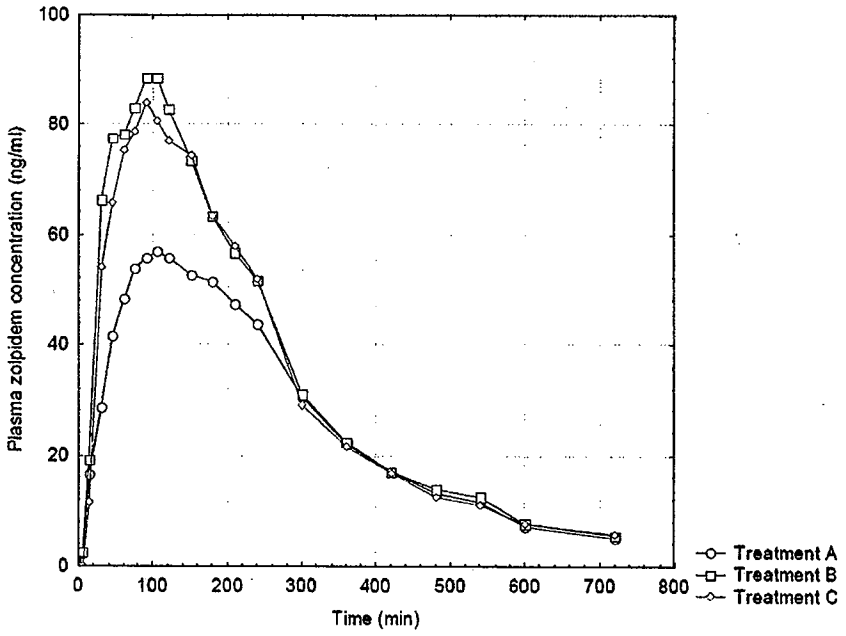
Sponsor has conducted a BE study comparing Formulation II with the reference Ambien® (Study OX22-005). Formulation II was found to be bioequivalent to the RLD Ambien®. However, Formulation II is not the to-be-marketed or commercial formulation. Therefore the Sponsor has also conducted a bridging BE study between Formulation II and the commercial formulation (Study OX22-008). Formulation II was bioequivalent to the commercial formulation, thereby establishing the link between the commercial formulation and the reference Ambien®.

A detailed summary of the bioequivalence studies are given below.

Study OX22-005: This study was conducted to establish bioequivalence between formulation II and the reference Ambien®.

Pharmacokinetic profile for different treatments is shown in the figure below.

Figure 1: Mean Plasma Concentrations of Zolpidem Following Administration of ——— and Ambien® Tablets b(4)



A = OX22 with meal, B = OX22 fasting, and C = Ambien® fasting

Following table represents PK parameters for different treatments.

Table 9: Non-Compartmental Pharmacokinetic Parameters mean of all individual values and (SD) of zolpidem under fasting conditions

Pharmacokinetic parameter	OX22 fasting	Ambien® fasting
AUC_{0-t} (min.ng/ml)	24295 (10046)	23077 (10992)
AUC_{0-f} (min.ng/ml)	25740 (11027)	24733 (12741)
C_{first} (ng/ml)	8.4 (9.9)	11.8 (18.5)
t_{first} * (min)	13.5 (5-17)	15.0 (5-60)
Cmax (ng/ml)	106.2 (42.7)	102.3 (41.7)
T_{max}* (min)	82 (30-180)	90 (30-180)
t1/2 (hr)	2.65 (0.58)	2.69 (0.83)

*Median (range)

Following table indicates primary pharmacokinetic parameters ratios and 90% confidence intervals levels.

Table 10: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Sponsor's Analysis)

b(4)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
FASTING/AMBIEN® FASTING	AUC_{0-t}	108.0	99.35	117.5
	$AUC_{0-\infty}$	107.6	98.6	117.5
	C_{max}	106.0	105.0	120.1

Reviewer's re-analysis of the data showed similar 90% confidence interval (CI), with the exception of lower boundary of 90% CI for Cmax; this being 91.7 in the reviewer analysis and 104.9 in the sponsor analysis. However 90% CIs were within acceptable limits, as shown in the table below.

Table 11: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence **Intervals (Reviewer's Analysis)**

b(4)

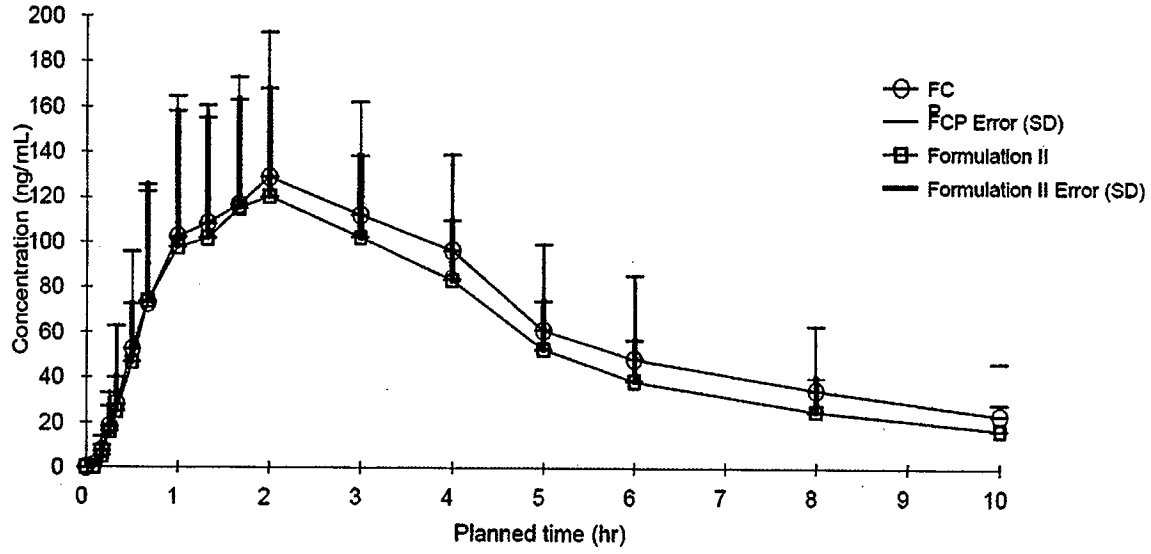
TREATMENT COMPARISONS	PARAMETER	RATIO	LOWER 90% CI	UPPER 90% CI
FASTING/AMBIEN® FASTING	$AUC_{0-\infty}$	107.6	98.6	117.5
	C_{MAX}	104.9	91.7	120.1

The results showed that, ——— **was bioequivalent to reference Ambien® under fasting conditions. The median tmax's were** 82 (range 30-180) minutes for formulation II and 90 (range: 30-180) minutes for Ambien® and these differences were not statistically significantly different. **b(4)**

Study OX22-008: This study was conducted to establish bridging link between formulation II and to-be-marketed formulation, final commercial product (FCP).

Pharmacokinetic profiles for different treatments are shown in the figure below.

Figure 2: Mean (N=18) Plasma Concentration versus Time Curve after Administration of Formulation II and Final Commercial Product (FCP)



Following table indicates the PK parameters for different treatments.

Table 12: Summary of Pharmacokinetic Variables of Formulation II and FCP

Parameter	Formulation II N = 18		Final Commercial Product (FCP) N = 18	
	Mean	SD	Mean	SD
AUC_{0-t} (ng*h/mL)	579.8	(222.5)	663.3	(310.1)
$AUC_{0-\infty}$ (ng*h/mL)	663.3	(287.3)	786.1	(443.5)
AUC_{0-30} (ng*h/mL)	8.85	(4.67)	10.06	(8.67)
AUC_{0-tmax} (ng*h/mL)	151.0	(82.8)	146.2	(86.1)
C_{max} (ng/mL)	133.40	(47.1)	148.39	(62.5)
C_{first} (ng/mL)	3.16	(3.08)	3.45	(4.29)
	Median	Range	Median	Range
t_{max} (h)	2.00	(1.00 - 4.00)	2.00	(0.33 - 3.00)
t_{first} (h)	0.17	(0.08 - 0.25)	0.17	(0.08 - 0.25)
$t_{1/2}$ (h)	2.89	(2.02 - 4.67)	2.68	(1.76 - 5.56)

Primary pharmacokinetic parameters used to **establish bioequivalence based on Sponsor's** analysis are presented in the following table.

Table 13: Treatment Comparisons for FCP versus Formulation II (Sponsor's analysis)

		90% Confidence Interval	
Pharmacokinetic variable	**Point estimate**	**Lower limit**	**Upper limit**
AUC_{0-t} (hr*ng/mL)[1)]	1.10	1.02	1.19
$AUC_{0-\infty}$ (hr*ng/mL)[1)]	1.12	1.01	1.23
C_{max} (ng/mL)[2)]	1.08	0.99	1.18

Reviewer's re-analysis of the data showed differences in the point estimate ratios and 90% confidence interval (CI) levels for lower boundary and upper boundary. However 90% CIs were within acceptable limits as shown in the table below.

Table 14: Pharmacokinetic Parameter Ratios of Point Estimates and 90% **Confidence Intervals (Reviewer's Analysis)**

Treatment Comparisons	**Parameter**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**
FCP/ Formulation II	$AUC_{0-\infty}$	1.12	0.8142	0.9863
	C_{max}	1.08	0.8453	1.0144

The results showed that formulation II was bioequivalent to final commercial product under fasting conditions. The median tmax's **were 120 (range: 60-240) minutes for** formulation II and 120 (range: 20-180) minutes for FCP and these differences were not statistically significantly different. Therefore establishing bridging link between formulation II and FCP.

What is the effect of food on the bioavailability —— **?**

b(4)

The effect of food on bioavailability was studied in study OX-005. This study was a single-center, three-period crossover, open-label, randomized study. The administration of sublingual tablet with food significantly decreased mean AUC and C_{max} —— **by** 20 and 30% respectively, while mean T_{max} was prolonged by 28% (from 82 to 105 minutes). Food also significantly decreased mean AUC and C_{max} of reference listed drug Ambien® by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 84 to 132 minutes). Effect of food on tmax was larger for Ambien® when compared to

Following table represents PK parameters of sublingual zolpidem under fasting and fed conditions. Please refer to figure 3, treatment A for PK profile.

Table 15: Non-Compartmental Pharmacokinetic Parameters mean of all individual values and (SD) ——— **under fasting and fed conditions** b(4)

Pharmacokinetic parameter	**OX22 fasting**	**OX22 with meal**
AUC0-t (min*ng/ml)	24295 (10046)	18847 (5645)
AUC0-f (min*ng/ml)	25740 (11027)	20097 (6764)
Cmax (ng/ml)	106.2 (42.7)	70.5 (18.8)
Tmax* (min)	82 (30-180)	105 (30-240)
t1/2 (hr)	2.65 (0.58)	2.39 (0.61)

Following table represents 90% CIs for sublingual zolpidem under fasting and fed conditions.

Table 16: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals

TREATMENT COMPARISONS	PARAMETER	RATIO	LOWER 90% CI	UPPER 90% CI
——— FED/ ——— FASTING	$AUC_{0-\infty}$	0.802	0.735	1.175
	C_{MAX}	0.688	0.601	0.876

b(4)

The results show that food significantly lowers bioavailability of sublingual zolpidem when compared to sublingual zolpidem under fasting conditions.

Are ——— 5 mg and 10 mg sublingual tablet formulations dose proportional? b(4)

Dose-proportionality of the zolpidem plasma concentrations resulting from the administration of the sublingual tablet 5 and 10 mg was determined in Study OX22-001 (using Formulation I). The results indicated that the sublingual tablet formulation was dose-proportional with respect to zolpidem PK parameters. Bioequivalence was established between formulation I and formulation II in terms of AUC and Cmax (Study OX22-004). However, tmax of formulation I was approximately 45% lower than formulation II as shown in the table below.

Summary of Pharmacokinetic Variables

Pharmacokinetic parameter	OX22 5 mg	OX22 10 mg
AUC 0-t (min•ng/ml)	14921.2 (6727.7)	30847.4 (14462.8)
AUC 0-∞ (min•ng/ml)	17209.5 (9079.9)	35245.5 (17839.6)
Cmax (ng/ml)	50.0 (20.8)	98.8 (32.7)
Tmax (min)	92.4 (42.9)	122.5 (58.3)

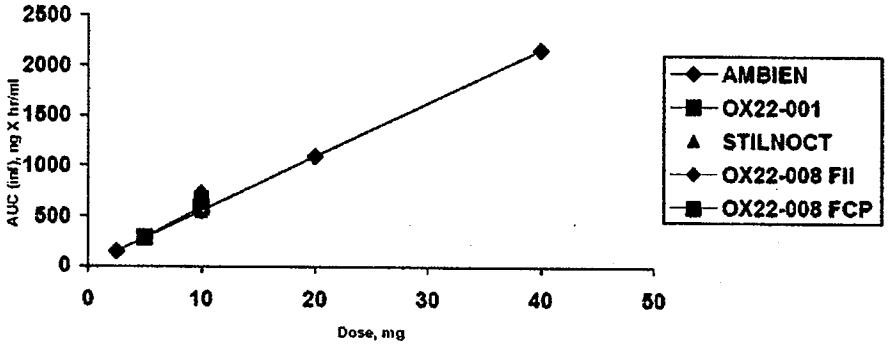
Comparison of dose normalized data for primary PK parameters to establish dose proportionality is shown in the following table.

Table 17: Comparison of Dose-Normalized Pharmacokinetic Parameters Following Single Oral Doses of Zolpidem Tartrate Sublingual Tablets 5 mg or 10 mg in Healthy Adult Volunteers

Parameter	Point Estimate	90% Confidence Intervals
AUC_{0-t}	1.0213	0.9265 - 1.1258
$AUC_{0-\infty}$	1.0189	0.8971 - 1.1572
C_{max}	1.0096	0.9205 - 1.1072

Sponsor also conducted linearity analysis using data from approval summary of Ambien® (NDA 19-908) and studies OX22-001, OX22-008. Following figure represents dose **proportionality** ——— **formulations** in comparison to Stilnoct® and RLD Ambien®. b(4)

Figure 14: Dose Linearity of oral and sublingual zolpidem products



The linearity analysis represents different study populations, different routes of administration and different analytical methodologies.

Does this application support lower dose (5 mg) zolpidem tartrate sublingual tablets for the geriatric and debilitated populations?

This application does not provide pharmacokinetic data in geriatric and debilitated populations using 5 mg ——— . The Sponsor completely relies on dose proportionality data and literature to support lower dose administration of sublingual zolpidem tartrate tablets in geriatric and debilitated populations. b(4)

Is there an early onset of absorption from sublingual ——— tablets when compared to reference Ambien®? b(4)

Minor differences between ——— and Ambien® in time to reach first detectable plasma concentration (t_{first}) and first detectable plasma concentration (C_{first}) parameters were observed. Zolpidem is detected earlier when administered by the sublingual route vs. the oral route. The differences between ——— and Ambien® under fasting conditions were statistically significantly different in study OX22-005. Mean and standard deviation values for t_{first} were 10.7 ± 5 min and 22.4 ± 15 min for ——— and Ambien® respectively. However, median t_{first} values were similar for ——— and Ambien® [13.5 (range: 5-17) minutes for ——— and median t_{first} values were 15 (range: 5-60) minutes for Ambien®]. There was also an overlap in the ranges. The C_{first} for ——— and Ambien® were 8.4 and 11.8 ng/ml, respectively. The sponsor also calculated the initial partial AUC to show higher exposures at 30 minutes post dose. The relevant concentrations/exposure for the onset of sleep is not known for zolpidem. b(4)

The following table shows the mean C_{first} and t_{first} from different studies.

Determination of mean (C_{first}) and (t_{first}) parameters in the OX22 clinical studies with healthy volunteers

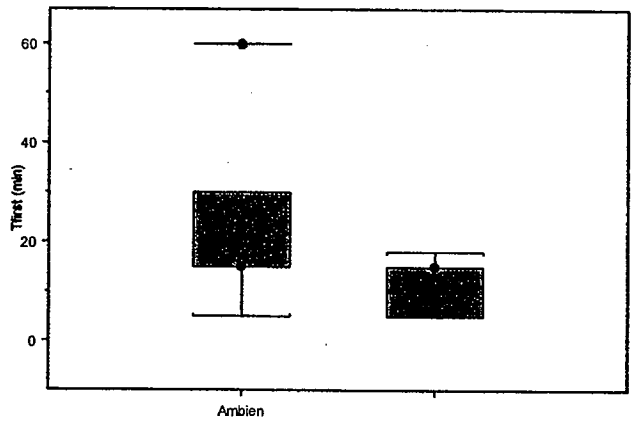
Study #	Dosage Form	Single Dose	C_{first} (ng/mL)	t_{first} (min)
OX001	FI OX22	5 mg	5.0	5.9
	FI OX22	10 mg	8.7	10.6
	Stilnoct®	10 mg	10.8	48.2
OX004	FII OX22	10mg	6.3	7.4
	FI OX22	10mg	9.2	7.5
OX005	FII OX22	10mg	3.9	8.4
	FII OX22	10mg	8.4	10.7
	Ambien®	10mg	11.8	22.4
OX008	FII OX22	10mg	3.16	9.0
	FCP OX22	10mg	3.45	8.4

According to the sponsor, the magnitude of the mean differences of approximately 10 minutes is comparable with the observed differences between ——— and Ambien® for sleep initiation (~10 minutes) in the pharmacodynamic study (Study OX22-006). However, Study OX22-006 was not adequately designed to show the differences in sleep onset as discussed in the review and the concentrations necessary for onset of sleep is not b(4)

established. The limited information at this time is only suggestive in nature and no definitive conclusions about higher exposures and earlier onset can be made at this time.

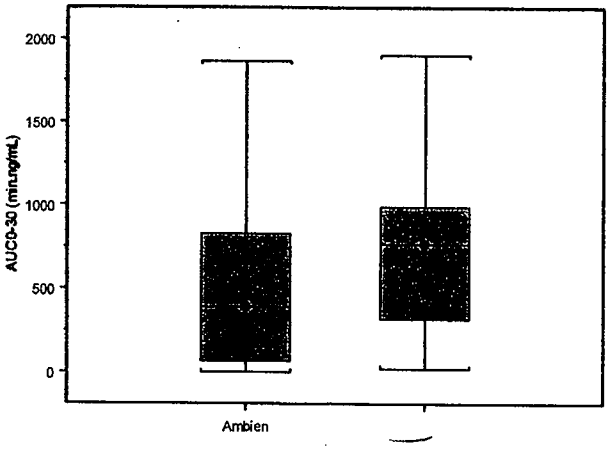
The following figures show the box plots of t_{first}, and partial exposures ($AUC_{0\text{-}30min}$ and $AUC_{0\text{-}60min}$) **for Ambien® and ——— from study OX22-005.** b(4)

Time to first detectable plasma concentration (T_{first})



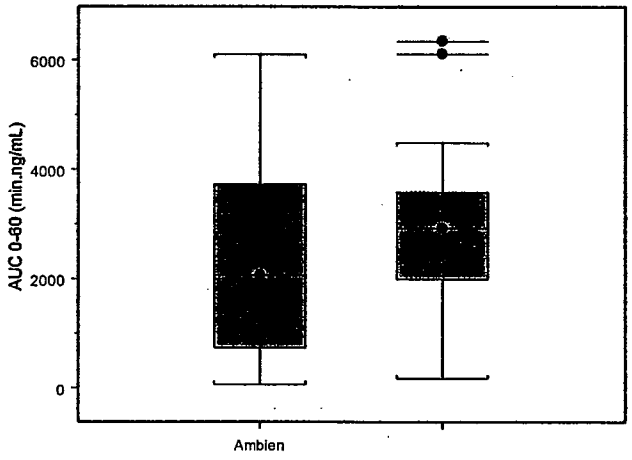
Tfirst values appear to be **earlier for ——— when compared to Ambien®. However** b(4) median tfirst values were similar and the ranges overlapped.

Partial exposure to zolpidem upto first 30 minutes



Mean and standard deviation values for partial exposures upto 30min ($AUC_{0\text{-}30min}$) were **766 ± 495 min.ng/mL and 545 ± 583 min.ng/mL for ——— and Ambien®** respectively. The mean $AUC_{0\text{-}30min}$ **for ——— was higher (40%) when compared to** b(4) $AUC_{0\text{-}30min}$ of Ambien®. However, the ranges overlapped for both treatments.

Partial exposure to zolpidem upto first 60 minutes



b(4)

Mean and standard deviation values for partial exposures upto 60 min ($AUC_{0\text{-}60min}$) were 2990 ± 1666 min.ng/mL and 2447 ± 1923 min.ng/mL for — and Ambien® respectively. The mean $AUC_{0\text{-}60min}$ for — was higher (22%) when compared to $AUC_{0\text{-}60min}$ of Ambien®. However, the ranges overlapped for — and Ambien®.

Is there a pharmacodynamic evidence of effectiveness of — to treat short term insomnia? b(4)

This NDA included a single dose pharmacodynamic study (study OX22-006). Hypnotic effects of sublingual zolpidem were compared with the reference Ambien® on sleep initiation, sleep continuity (maintenance), as well as on the patients' subjective assessments and the next day residual effects. This study was conducted using formulation II.

Following table indicates the results of primary end points of sleep initiation and sleep maintenance.

Table 18: Polysomnography Sleep Parameter Results

Variables*	Baseline	Zolpidem tartarate sublingual tablets10 mg (min)	Ambien® 10 mg (min)	Treatment Differences	
				Estimates (± SD) (minutes)	p-value
Sleep Initiation					
LPS	84.54 ± 40.35	19.76 ± 15.55	30.06 ± 23.48	-10.2823 ± 2.98	0.0010
ST1-L	72.30 ± 39.32	17.66 ± 13.37	26.31 ± 22.72	-8.6307 ± 2.80	0.0030
SOL	61.07 ±	13.94 ± 12.67	21.35 ±	-7.4273 ± 2.24	0.0047

	34.64		20.30		
Sleep Maintenance (Continuity)					Confidence Intervals (Minutes)
TST	324.29± 46.52	432.06 ± 29.30	424.72 ± 34.42	7.2243 ± 3.60	(0.0213, 14.4272)
WASO	84.08 ± 36.16	30.87 ± 27.79	29.82 ± 26.80	1.1250 ± 3.08	(-5.0293, 7.2793)

*The variables are expressed in minutes (mean ±SD).

Next day subjective assessment of residual effects include Visual Analogue Scale (VAS) for assessment of alertness, contentedness and calmness, Digit Symbol Substitution Test (DSST) for attention and concentration, Leeds psychomotor tests (MCRT and CFFT)-attention abilities and vigilance.

The results showed that compared to Ambien®, — **significantly shortened the** primary end points, sleep initiation (LPS) and two secondary sleep initiation endpoints **(SOL and ST1L). However, for** — the two other endpoints of the primary objectives wake after sleep onset (WASO) and total sleep time (TST) indicated that there were no differences in these parameters. Sleep subjective assessment of residual effect parameters, digital symbol substitution test, visual analogue scales, Leeds psychomotor test-multiple choice reaction time and critical flicker fusion test indicated no significant treatment effect. b(4)

E. Analytical

Have the analytical methods been sufficiently validated?

Yes.

Method: Plasma zolpidem concentrations were determined at two different laboratories using different methods as discribed below. Plasma samples from studies OX22-001 and OX22-004 were analyzed at — (method I) and plasma samples from OX22-005 and OX22-008 were analyzed at — institute (method II). b(4)

Method I: The analytical procedure for determination of zolpidem in human plasma has been validated. The method involves isolation of the parent drug by solid phase extraction using cartridges. The eluate is injected onto a reversed phase column with a mobile phase composed of acetonitrile: 50 mM potassium phosphate buffer at pH 6.0 and determined by fluorescence detection. The method was validated in the range 1.0-400 ng/ml with a lower limit of quantification of 1.0 ng/ml using a 0.5 ml sample volume.

Validation Summary for Zolpidem Detection by HPLC with Fluorescence

b(4)

Laboratory	—
Analyte	Zolpidem
Internal Standard (IS)	—
Method description	HPLC-reverse phase liquid chromatography with fluorescence detection
Limit of quantitation (ng/mL)	1.0

Average recovery of drug (%) Average recovery of IS	122 Not performed
Standard curve concentration range (ng/mL)	1 - 400
Standard Accuracy Range (%)	**-11.4 – 12.6**
Standards Precision Range (%)	**0.9 – 10.2**
QC concentrations (ng/ml)	LQC = 3.0 MQC = 30 HQC = 300
QC precision range (CV %)	**Inter Assay: 2.8 – 6.4** **Intra Assay: 2.4 – 5.6**
QC accuracy (%)	Mean: LQC:-2.8 MQC:7.0 HQC: -1.5 **Range: LQC: -13.3 – 11.3** **MQC: 1.3 – 12.7** **HQC: - 8.7 – 7.3**
Bench-top stability (plasma)	4 hours at room temperature
Long-term storage stability (plasma)	178 days at -20 °C
Freeze-thaw stability	3 cycles
Stock solution stability at RT	6 hours
Long-term stock solution stability in 2 – 8 °C	106 days
Short term stock solution stability in 2 – 8 °C	Not performed
In injector stability (hrs) Wet extract stability	19 hours at 12 °C Not performed , see injector stability
Dilution integrity	2.5 times of C8 conc. (1000 ng/mL) diluted 10:90 CV: 2.1 % Accuracy: - 3.8 %
Selectivity	No interfering peaks observed

Method II: Plasma samples were spiked with internal standard ~~—~~ and b(4)
followed by addition of ammonium chloride buffer and then subjected to liquid-liquid extraction. Organic phase was separated, dried and reconstituted with mobile phase. Samples were analyzed using LC-MS/MS system.

Validation Summary for Zolpidem Detection by LC-MS/MS

b(4)

Laboratory	~~—~~
Analyte Internal Standard (IS)	~~—~~
Method description	Reverse phase liquid chromatography with Tandem Mass Spectrometric detection
Limit of quantitation (ng/mL) Average recovery of drug (%) Average recovery of IS	0.5 Not performed Not performed
Standard curve concentration range (ng/mL)	**Range 1: 0.52 – 34**
Standard Accuracy Range (%)	**Range 2: 34 – 582 Range 1: -12 – 376**

Standards Precision Range (%)	**Range 2: -19 – 12 Range 1: 0.44 – 17.37**
	Range 2: 1.1 – 9.7
QC concentrations (ng/ml)	Range 1: LQC = 0.56 HQC = 1.5 Range 2: LQC = 205 HQC = 403
QC precision range (CV %)	**Inter Assay: 2.8 – 9.6**
QC accuracy range (%)	**Range 1: 0.56 ng/ml: -7 – 20** **1.5 ng/ml: 0 – 7** **Range 2: 205 ng/ml: 4 – 10** **403 ng/ml: -3 – 12**
Bench-top stability (plasma) Long-term storage stability (plasma)	4 hours at room temperature 178 days at -20 °C
Freeze-thaw stability	4 cycles
Stock solution stability at RT	6 hours
Long-term stock solution stability in 2 – 8 °C	106 days
Short term stability in 2 – 8 °C	Not performed
In injector stability (hrs)	Not performed
Wet extract stability	Not performed
Dilution integrity	2 times of C6 conc. (range 2) 1056 ng/mL diluted 10:90 CV: 1.1 % Accuracy (mean): - 6.2 %
Selectivity	From 5 different blank subjects, highest interfering peak 12.8 % of lowest calibrator

III. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert **labeling** —— **and finds it acceptable** pending the following revision: b(4)

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

31 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

IV. APPENDIX

A Individual Study Synopsis

OX22-001: An open randomized three-period crossover single-centre study to evaluate the pharmacokinetic profile of sublingual zolpidem 5 mg and 10 mg, and of oral zolpidem (Stilnoct®) 10 mg

Study Title	An open randomized three-period crossover single-centre study to evaluate the pharmacokinetic profile of sublingual zolpidem 5 mg and 10 mg, and of oral zolpidem (Stilnoct®) 10 mg
Study number	OX22-001
Study Period	June 02, 2004 to June 23, 2004
Study Director	Bo-Lennart Johansson, MD, PhD
Study Design	Single-centre, open, randomized, three-period crossover trial

Study Population: N=18,
Age: 18-40 years
Gender: Healthy Male or Female

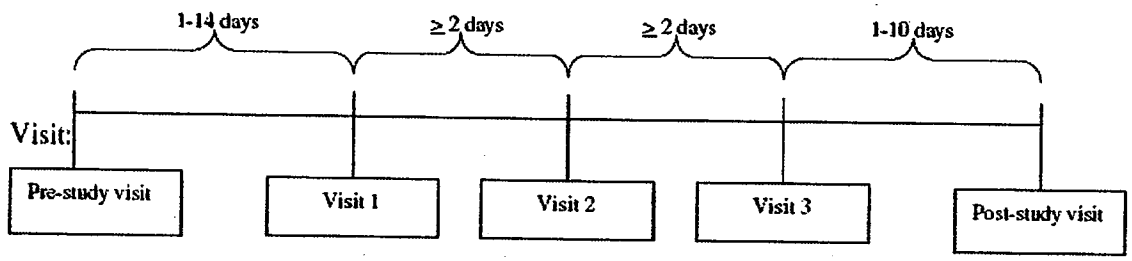
Objectives

To compare bioavailability of sublingual zolpidem 10 mg (formulation I)and oral zolpidem (Stilnoct®) 10 mg and to compare bioavailability with regard to dose proportionality between two doses of sublingual zolpidem; 5 mg and 10 mg, to prove linearity. The primary variable is AUC_{0-t}.

Study Design: This study was conducted as a single-centre, open, randomized, three-period crossover trial to evaluate and compare the bioavailability of OX22 (5 mg and 10 mg) to Stilnoct® (10 mg). The three study drug administrations were to be given to each of the 18 healthy volunteer subjects in random order at visit 1, 2 and 3. Visit 1 and 2 were to be followed by a wash-out period of at least 2 days.

At the pre-entry the subjects had a full clinical examination including medical history, physical examination, ECG, routine haematology and clinical chemistry, drug and alcohol screen. The pre-study visit was to be performed within 14 days before Visit 1.

Figure 4: Study Design



Treatment Groups: **Treatment 1 "A": Sublingual** Zolpidem OX22 (Test) 5 mg
Treatment 2 "B": Sublingual Zolpidem OX22 (Test) 10 mg
Treatment 3 "C": Stilnoct (oral zolipidem) 10 mg (Reference)

Washout period was at least 2 days

Method of Assigning Subjects to Treatment Groups (Randomization and Subject Assignment)

This study was randomized. Subject eligibility was to be established before treatment randomization. Confirmed eligible subjects were to be assigned a subject number in a consecutive order. Each subject number was randomized to one of six possible treatment sequences (3x2x1) according to a computer generated randomization list provided by the study statistician. Discontinued subjects were to be replaced with a new subject in order to have eighteen subjects completing the study, three on each treatment sequence. Substituting subjects were to be given a new subject number and receive study treatment in the same treatment sequence as the replaced subjects.

Selection of doses in the study

The OX22 doses 5 mg and 10 mg were chosen. For adults below the age of 65 the recommended oral tablet dose is 10 mg. For Stilnoct® the 10 mg dose was chosen, in **accordance with the manufacturer's recommendations.**

Sampling: Blood samples (7 ml each) for determination of zolpidem in plasma were to be collected immediately before (0 minutes) and at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480 and 600 minutes after study drug administration.

Determination of zolpidem in plasma samples

Zolpidem in human plasma was determined by HPLC with fluorescence detection. Zolpidem and an internal standard were purified from human heparin plasma by solid phase extraction using C18 cartridges, rinsed with water and eluted with methanol. The eluate was injected onto a reversed phase C18 LC column (150 x 4.6 mm, 5 µm) with a mobile phase composed of acetonitrile: 50 mM potassium phosphate buffer at pH 6.0 (4:6, v/v) and determined by fluorescence detection (excitation at 254 nm and emission at 400 nm). The lower limit of quantification was 1.0 ng/ml for zolpidem in human plasma. The mean accuracy of the assay as determined from the analysis of QC samples was within ±10.0%.

The method was validated in the range 1.0-400 ng/ml with a lower limit of quantification of 1.0 ng/ml using 500 µl sample volume. The concentration of zolpidem was determined in a total of 809 human plasma samples. The assay performance during the study is given in the table below.

Table 19: Assay performance during the study

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	3.0, 30 and 300 ng/mL	1.0, 3.0, 10, 25, 50, 100, 250, 400 ng/mL
Between Batch Precision (%CV)	6.1 – 11.6	3.3 -8.0
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9961	
Linear Range (ng/mL)	1.0 – 400 ng/mL	
Sensitivity (LLOQ, ng/mL)	1.0 ng/mL	

Pharmacokinetic Measurements:

Area under the plasma concentration time curve from time zero to the last quantifiable sampling point (AUC_{0-t}). Area under the plasma concentration time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), area under the plasma concentration time curve from time 0 to time 30 minutes (AUC_{0-30}), area under the plasma concentration time curve from time 0 to maximal plasma concentration (minutes) [AUC0- t_{max}], time to the first measurable plasma concentration (t_{first}), time to maximal plasma concentration (tmax), terminal elimination half-life (terminal t1/2), first measurable plasma concentration (C_{first}) and maximum plasma concentration (C_{max}) were compared between the treatments.

Statistical Methods:
Bioequivalence: Log dose adjusted AUC were analyzed by analysis of variance using the SAS statistical program with subject, treatment and period as class variables. Differences between treatments were to be given as 90% confidence intervals (CI). Equivalence could be proved if the 90% CI of the geometric mean ratio was within 0.80 and 1.25).

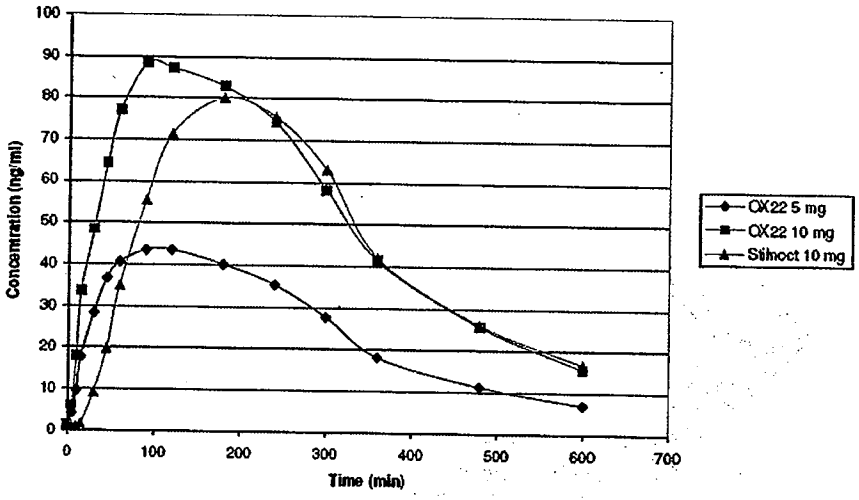
Dose proportionality - Linearity: Log dose adjusted AUC were analyzed by analysis of variance using the SAS statistical program with subject, treatment and period as class variables. Differences between treatments were to be given as 90% CI. Dose proportionality could be proved if the 90% CI for the difference between doses did not exceed ±20% (or the 90% CI of the geometric mean ratio was within 0.80 and 1.25).

Secondary objectives and variables ($AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, t_{first}, C_{first} and efficacy variables) were to be analyzed by analysis of variance using the SAS statistical program with subject, treatment and period as class variables. 90% CI of the geometric mean ratio for $AUC_{0-\infty}$ and C_{max} were also calculated.

RESULTS

All randomized subjects were included in the analysis (n=18, 10 Male and 8 Female).

Figure 5: Mean Plasma Concentration-Time Curves



Bioequivalence criteria were not met between OX22 10 mg and Stilnoct® 10 mg.

Bioequivalence between OX22 10 mg and Stilnoct® 10 mg for AUC_{0-t} was not established. The 90% confidence interval (CI) for the geometric mean ratio (OX22 10mg/Stilnoct® 10 mg) for AUC_{0-t} (1.0767; 1.2734) exceeds the upper limit (0.8; 1.25). The upper value of the corresponding CI for AUC_{0-inf} is (1.0276; 1.2792). The 90% CI for C_{max} (1.0095; 1.2207) is inside the pre-specified limits (0.8; 1.25).

PK Variable	Ratio	90%CIs	
AUC_{0-t}	1.172	1.0767	[redacted]
AUC_{0-inf}	1.146	1.0276	[redacted]
C_{max}	1.105	1.0095	1.2207

Dose proportionality between OX22 5 mg and 10 mg for dose adjusted AUC0-t was established. Comparison of dose normalized data for primary PK parameters to establish dose proportionality is shown in the following table.

Table 20: Comparison of Dose-Normalized Pharmacokinetic Parameters Following Single Oral Doses of Zolpidem Tartrate Sublingual Tablets 5 mg or 10 mg in Healthy Adult Volunteers

PARAMETER	POINT ESTIMATE	90% CONFIDENCE INTERVALS
AUC_{0-t}	1.0213	0.9265 - 1.1258
$AUC_{0-\infty}$	1.0189	0.8971 - 1.1572
C_{max}	1.0096	0.9205 - 1.1072

The time to the first measurable plasma concentration, tfirst and the time to the maximum plasma concentration, tmax are significantly shorter for OX22 10 mg, compared to Stilnoct® 10 mg ($p<0.0001$ and $p=0.0165$, respectively). The elimination half-life ($t_{1/2}$) of zolpidem was similar for OX22 5 mg and 10 mg (2.85 and 2.71 hours, respectively)

Pharmacokinetic parameter summary is presented in the following table.

Table 21: Summary of Pharmacokinetic parameters mean and (SD) of zolpidem following sublingual and oral administration (n=18).

Pharmacokinetic parameter	OX22 5 mg	OX22 10 mg	Stilnoct® 10 mg
AUC 0-t (min•ng/ml)	14921.2 (6727.7)	30847.4 (14462.8)	26858.8 (14607.1)
AUC 0-∞ (min•ng/ml)	17209.5 (9079.9)	35245.5 (17839.6)	32485.2 (22577.2)
Cfirst (ng/ml)	5.0 (2.9)	8.7 (5.8)	10.8 (11.5)
tfirst (min)	5.9 (2.4)	6.6 (2.3)	48.2 (34.6)
Cmax (ng/ml)	50.0 (20.8)	98.8 (32.7)	90.6 (35.1)
Tmax (min)	92.4 (42.9)	122.5 (58.3)	177.5 (80.2)
t1/2 (h)	2.85 (1.22)	2.71 (0.98)	2.74 (1.31)

Mean tmax was shorter for OX22 10 mg when compared to Stilnoct 10 mg (approximately 55 minutes).

The mean Cmax achieved after administration of 10 mg OX22 and Stilnoct was comparable.

Conclusions

- Bioequivalence criteria were not met when the pharmacokinetics of OX22 10 mg, compared to Stilnoct® 10 mg, were compared with regard to AUC0-t, AUC0-∞ as upper limits of confidence intervals were above 125%.
- Time to reach the maximum plasma concentration, (T_{max}) was significantly shorter for OX22 10 mg, compared to Stilnoct® 10 mg.

OX22-004: An open randomized two-period crossover study to assess the bioavailability of sublingual zolpidem for the treatment of short-term insomnia

Study Title	An open randomized two-period crossover study to assess the bioavailability of sublingual zolpidem for the treatment of short-term insomnia
Study number	OX22-004
Study Period	June 21, 2005 to July 13, 2005
Study Director	Pierre Lafolie, MD, PhD
Study Design	Single-centre, open, randomized, two-period crossover trial

Study Population: N=12,
Age: 18-40 years
Gender: Healthy Male or Female

Objectives

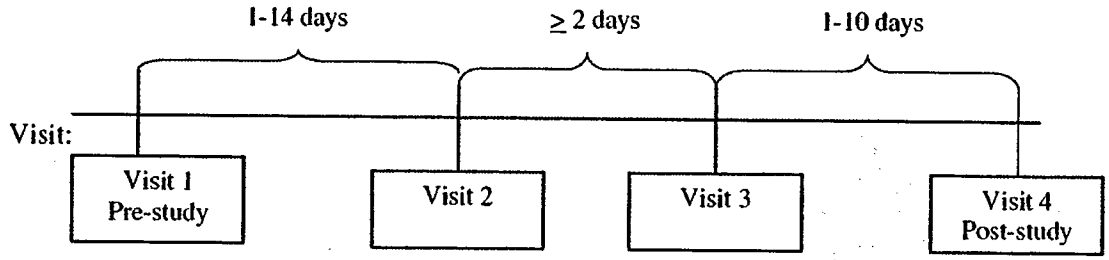
To compare the bioavailability of an optimised pharmacological composition of sublingual zolpidem (Formulation II) with a previously developed sublingual zolpidem composition (Formulation I, reference), given as single doses

Study Design: This study was conducted as a single-centre, open, randomized, two-period crossover trial to compare the bioavailability of sublingual zolpidem 10 mg. The two study drug administrations given to the subjects in random order at Visit 2 and 3. Visit 2 and 3 were separated by a wash-out period of at least 2 days.

At the pre-study Visit 1, the subjects had a full clinical examination including medical history, physical examination, ECG, routine haematology and clinical chemistry, drug and alcohol screen. The pre-study visit was to be performed within 14 days before Visit 2.

Before each study day (Visit 2 and 3) the subjects were fasted at least 8 hours before until four hours after zolpidem administration. Standardized lunch and dinner were served during the study days. Each subject consumed the same quantity of food during the study days. The subjects were allowed to drink water ad libitum during the study days, except for the 60 minutes pre and post zolpidem administration.

Study Design



Treatment Groups: Treatment 1 "A": Sublingual Zolpidem (Formulation II)10 mg (Test)
Treatment 2 "B": Sublingual Zolpidem (Formulation I) 10 mg (Reference)

Washout period was at least 2 days

Duration of treatment:
Subjects were administered one dose of OX22, Treatment A followed by one dose of Treatment B or vice versa, at Visit 2 and Visit 3. There was a wash-out of at least 2 days between the two treatment visits.

Treatment Instructions
The study medication was placed under the subject's tongue by the study nurse. The zolpidem sublingual tablets were placed directly under the tongue into the deepest part of the oral cavity. It was instructed that the subjects did not move or touch the tablet once it had attached to the mucous membrane. Subjects were also instructed not to swallow the tablet, allowing it to dissolve under the tongue without chewing or sucking. Water was not allowed from one hour before to one hour after dose administration. The time of dose administration commenced when the tablet was placed under the tongue. The subjects were to keep their mouth shut and not deliberately move their tongue for at least 15 minutes.

Method of Assigning Subjects to Treatment Groups (Randomization and Subject Assignment)

This is a randomized study. Confirmed eligible subjects were assigned a subject number in a strictly consecutive order. Each subject number was randomized to one of two possible treatment sequences according to a computer generated randomization list provided by the study statistician. Discontinued subjects were to be replaced with a new subject in order to have twelve subjects completing the study, six on each treatment sequence. Substituting subjects were to be given a new subject number and receive study treatment in the same treatment sequence as the replaced subjects.

Selection of Doses in the Study

Zolpidem dose 10 mg was chosen. This corresponds to the recommended oral dose was 10 mg for adults below the age of 65.

Sampling: Blood samples (5 ml each) for determination of zolpidem in plasma were to be collected at 15 occasions on each study day. Samples were to be collected immediately before (0-15 minutes) and at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480 and 600 minutes after study drug administration.

Sample analysis

Zolpidem in human plasma was determined by HPLC with fluorescence detection. Zolpidem and an internal standard —— were purified from human heparin plasma by solid phase extraction using —— C18 cartridges, rinsed with water and eluted with methanol. The eluate was injected onto a reversed phase C18 LC column (150 x 4.6 mm, 5 µm) with a mobile phase composed of acetonitrile: 50 mM potassium phosphate buffer at pH 6.0 (4:6, v/v) and determined by fluorescence detection (excitation at 254 nm and emission at 400 nm). The lower limit of quantification was 1.0 ng/ml for zolpidem in human plasma. The mean accuracy of the assay as determined from the analysis of QC samples was within ±10.0%. b(4)

The method was validated in the range 1.0-400 ng/ml with a lower limit of quantification of 1.0 ng/ml using 500 µl sample volume. The assay performance during the study is given in the table below.

Table 22: Assay performance during the study

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	3.0, 30 and 300 ng/mL	1.0, 3.0, 10, 25, 50, 100, 250, 400 ng/mL
Between Batch Precision (%CV)	**3.9 – 11.9**	**2.0 -10.8**
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9989	
Linear Range (ng/mL)	**1.0 – 400 ng/mL**	
Sensitivity (LLOQ, ng/mL)	1.0 ng/mL	

Pharmacokinetic Measurements:

Area under the plasma concentration time curve from time zero to the last quantifiable sampling point (AUC_{0-t}). Area under the plasma concentration time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), area under the plasma concentration time curve from time 0 to time 30 minutes (AUC_{0-30}), area under the plasma concentration time curve from time 0 to maximal plasma concentration (minutes) [AUC0- t_{max}], time to the first measurable plasma concentration (t_{first}), time to maximal plasma concentration (tmax), terminal elimination half-life (terminal t1/2), first measurable plasma concentration (C_{first}) and maximum plasma concentration (C_{max}) were compared between the treatments.

Statistical methods:
Log transformed parameters for both area under the plasma concentration time curve (AUC) and Cmax were analyzed using an analysis of variance (ANOVA) model with sequence, period and treatment as class variables, and subject (sequence) as a random effect. Differences between treatments were given as 90% confidence intervals (CIs) for

the geometric mean ratios, calculated using the adjusted means (LSMEANS) from the analysis of variance (ANOVA) of log-transformed data with subsequent exponential transformation. Equivalence was proven if the 90% CI for the geometric mean ratio B/A for the primary variable AUC0-t was within the limits 0.80 and 1.25.

RESULTS

All randomized subjects were included in the analysis (n=12, 8 Male and 4 Female).

Figure 6: Mean Plasma Concentration-Time Curves After Administration of New Formulation (A or II) and Previously Developed Formulation (B or I)

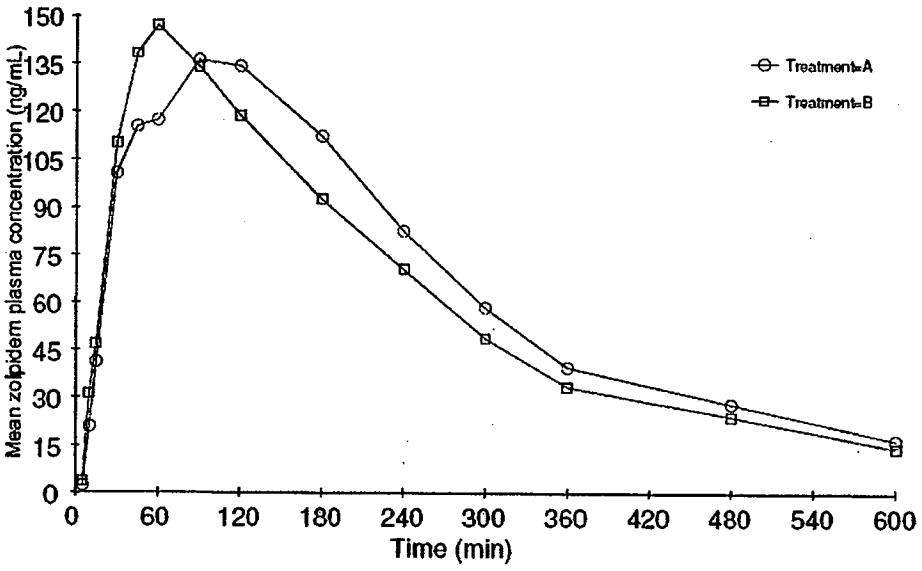


Table 23: Treatment Comparisons for Treatment A versus Treatment B

		90% Confidence Interval	
Pharmacokinetic variable	**Point estimate**	**Lower limit**	**Upper limit**
AUC_{0-t} (hr*ng/mL)	1.077	0.996	1.164
$AUC_{0-\infty}$ (hr*ng/mL)	1.083	0.997	1.176
Cmax $(ng/mL)^2$	0.981	0.877	1.098

Table 24: Summary of Pharmacokinetic Variables

Pharmacokinetic parameter	OX 22 10 mg Formulation II	OX 22 10 mg Formulation I
AUC_{0-t} (min.ng/ml)	39650 (14970)	36500 (140
$AUC_{0-\infty}$ (min.ng/ml)	44330 (18200)	40460 (167

C_{first} (ng/ml)	6.328 (7.532)	9.172 (8.936)
t_{first} (min)	7.4 (3.3)	7.5 (3.4)
C_{max} (ng/ml)	166.4 (41.5)	169.3 (42.9)
t_{max} (min)	93.8 (50.5)	48.3 (21.1)
$t_{1/2}$ (h)	2.781 (0.792)	2.827 (0.735)

Reviewer's Comment: Tmax of formulation I in this study is shorter (approximately 45% shorter) when compared to Tmax of sublingual zolpidem (Formulation I) in study OX22-001.

Conclusions

- Time to reach the maximum plasma concentration, (T_{max}) was significantly shorter for Formulation I compared to Formulation II.
- Bioequivalence was established between Formulation I and Formulation II of sublingual zolpidem 10 mg.

OX22-005: An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for the treatment of short-term insomnia

Study Title	An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for the treatment of short-term insomnia
Study number	OX22-005
Study Period	October 3, 2006 to November 2, 2006
Study Director	Pierre Lafolie, MD, PhD
Study Design	Single-centre, open, randomized, three-period crossover trial

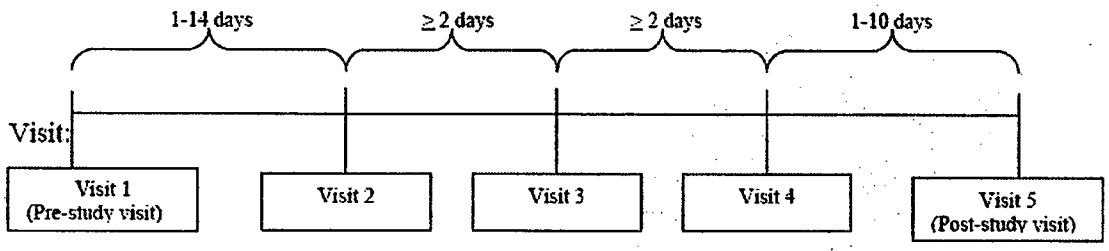
Study Population: N=18,
Age: 18-65 years
Gender: Healthy Male or Female

Objectives

- To assess and compare the pharmacokinetic profile (bioequivalence) of sublingual **zolpidem** —— **10 mg) and oral** zolpidem (Ambien® 10 mg, reference) both given as a single doses after fasting. b(4)
- To compare the pharmacokinetic profile (to test for a difference) of sublingual **zolpidem** —— **10 mg) given as single** doses immediately after a meal or after fasting.
- To compare the pharmacokinetic profile (to test for a difference) of sublingual **zolpidem** —— **10 mg) given as a single** dose immediately after meal, and oral zolpidem (Ambien® 10 mg, reference) given as a single doses after fasting.
- To assess tolerability and safety of treatments

Study Design: This study was conducted as a single-centre, open, randomized, three-period crossover trial to evaluate and compare the PK profile of sublingual zolpidem b(4)
(_____; OX22) 10 mg, given with and without concomitant food intake, and oral zolpidem (Ambien®) 10 mg, given without food.

Figure 1: Overall study design



Treatment Groups: Treatment 1 "A" : _____ 10 mg (fed) b(4)
Treatment 2 "B" : _____ 10 mg (fasting)
Treatment 3 "C" : Ambien tablet 10 mg (fasting)

Washout period was ≥2 days

Treatment Instructions

_____ sublingual tablets were placed directly under the tongue into the deepest part b(4)
of the oral cavity. Instructions were given to the subjects not to move or touch the tablet once it was administered, not to swallow the tablet, allowing it to dissolve under the tongue without chewing or sucking. Water was not allowed from one hour before to one hour after dose administration. The time of dose administration commenced when the tablet was placed under the tongue. The subjects were to keep their mouth shut and were instructed not to move their tongue for at least 15 minutes or until the tablet was dissolved. Ambien®, oral tablets, were to be swallowed with a glass of tap water (200 ml).

Method of Assigning Subjects to Treatment Groups (Randomization and Subject Assignment)

This is a randomized study. Each subject number was randomized to one of six possible treatment sequences according to a computer generated randomization list provided by the study statistician. Discontinued subjects were to be replaced with a new subject in order to have eighteen subjects completing the study, three on each treatment sequence.

Eighteen subjects were enrolled, three on each treatment sequence. The subjects were consecutively randomized to one of following 6 treatment sequences. ABC, ACB, BAC, BCA, CAB, CBA.

Selection of Doses in the Study

Zolpidem dose 10 mg was chosen since the recommended oral dose was 10 mg for adults below the age of 65.

Sampling: Blood samples (5 ml each) for determination of zolpidem in plasma were collected at immediately before (-15-0 minutes) and at 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600 and 720 minutes after study drug administration.

Sample analysis

The concentration of zolpidem was determined using a liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) system. To the plasma samples (500 µl), 50 µl of water and 50 µl of internal standard _____ were added, followed by 1.0 ml of ammonium chloride buffer (20 mM, pH 9.3). Liquid-liquid extraction was then performed with 5.0 ml of ethylacetate/dichloromethane 50/50 v/v. The organic phase was removed and evaporated to dryness under a gentle stream of nitrogen at 50 °C. The samples were then reconstituted in 50 µl of aqueous formic acid (0.2%)/methanol 50/50 v/v and transferred to vials for injection into the LC-MS/MS system. The lower limit of quantification was 0.5 ng/ml. Assay performance during the study is summarized in the following table. b(4)

Table 25: Assay performance during the study

Parameter	Quality Control Samples	Standard Curve Samples
Quality Control or Standard Curve Concentration (ng/mL)	1.5, 205, and 403 ng/mL	Range 1: 0.52, 1.0, 2.1, 3.4, 5.2, 8.4, 15, 34 ng/mL Range 2: 34, 66, 106, 169, 262, 528 ng/mL
Between Batch Precision (%CV)	**6.0 – 11.8**	**Range 1: 0.7 – 28.81 Range 2: 0.84 – 12 95**
Linearity	Weighted linear equation ($1/X^2$), Range 1: mean r =0.9994, Range 2: mean r= 0.9995	
Linear Range (ng/mL)	**0.52 – 528 ng/mL**	
Sensitivity (LLOQ, ng/mL)	0.5 ng/mL	

Pharmacokinetic Measurements:

Pharmacokinetic Parameters Assessed

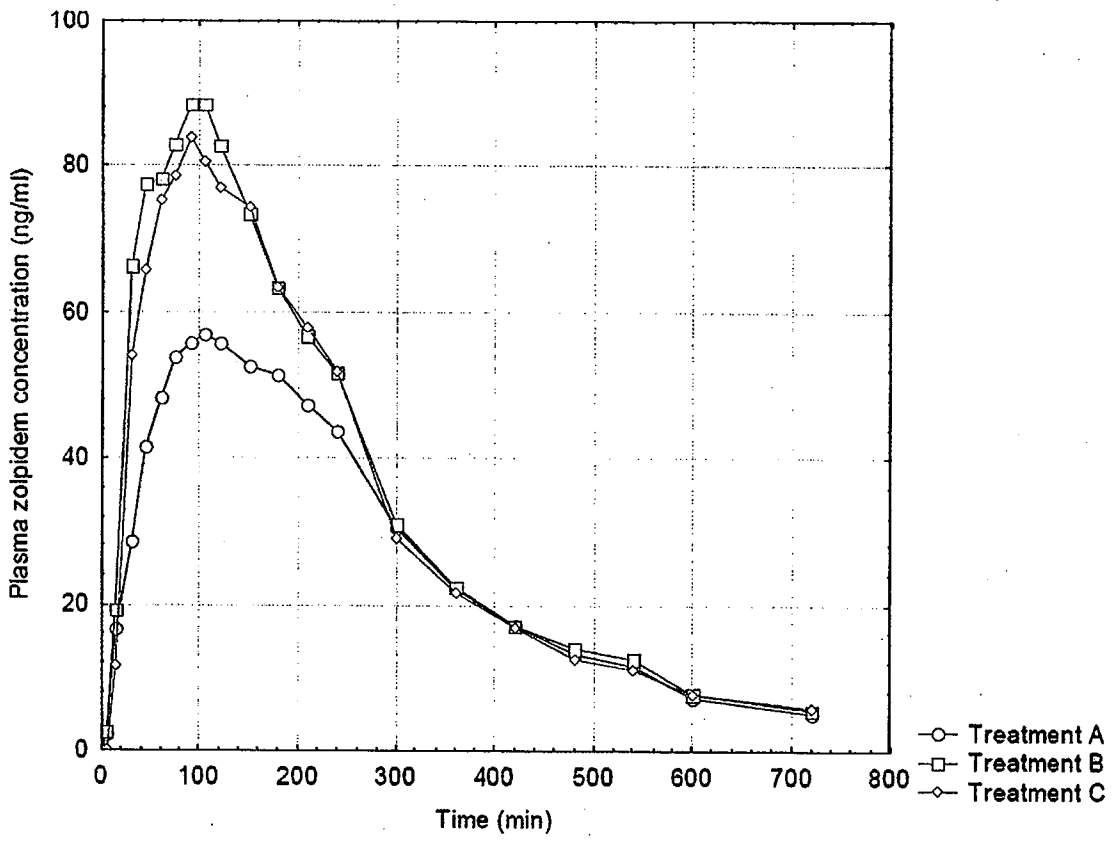
The AUC to the last measurable observation (AUC_{0-T}) and extrapolated to infinity ($AUC_{0-\infty}$), C_{max}, T_{max}, $t_{1/2,z}$, C_{first}, AUC_{0-30}, AUC_{0-tmax} and AUC_{0-60}. The concentration versus time data was used to calculate the AUC between consecutive blood drug levels. AUC_{0-T} was to be calculated from zero time to the last non-zero concentration (C_{Tlast}) by using the linear trapezoidal method.

RESULTS

Bioequivalence: Bioequivalence criteria are met between ——— fasting and Ambien® fasting. The geometric mean ratio ——— fasting/Ambien® fasting for the AUC_{0-t} was 1.08 with 90% CI = (0.99, 1.17). Cmax geometric mean ratio was 1.05 with 90% CI = (0.92, 1.20). b(4)

Pharmacokinetic profile for different treatments is shown in the figure below.

Figure 7: Mean Plasma Concentrations of Zolpidem Following Administration of ——— and Ambien® Tablets



A = OX22 with meal, B = OX22 fasting, and C = Ambien® fasting

Median tmax was shorter for ——— fasting (82 min), Ambien® fasting was at 90 min, although ranges (range: 30-180 min) overlapped. Tmax values for ——— versus Ambien® under fasted conditions were not statistically significant. b(4)

Table 26: Non-Compartmental Pharmacokinetic Parameters Mean of all Individual Values and (SD) of Zolpidem

Pharmacokinetic parameter	OX22 fasting	Ambien® fasting
AUC_{0-t} (min.ng/ml)	24295 (10046)	23077 (10992)

AUC_{0-f} (min.ng/ml)	25740 (11027)	24733 (12741)
C_{first} (ng/ml)	8.4 (9.9)	11.8 (18.5)
t_{first} * (min)	13.5 (5-17)	15.0 (5-60)
Cmax (ng/ml)	106.2 (42.7)	102.3 (41.7)
T_{max}* (min)	82 (30-180)	90 (30-180)
t1/2 (hr)	2.65 (0.58)	2.69 (0.83)

*Median (range)

Primary pharmacokinetic parameters used to establish bioequivalence are presented in the following table based on sponsor's analysis.

Table 27: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
——— Fasting/Ambien® Fasting	AUC_{0-t}	1.0804	0.9935	1.1749
	$AUC_{0-\infty}$	1.0765	0.9862	1.1754
	C_{max}	1.060	1.0497	1.2011

b(4)

Reviewer's re-analysis of the data showed similar 90% confidence interval (CI), with the exception of lower boundary of 90% CI for Cmax being 0.917 in the reviewer analysis and 1.049 in the sponsor analysis. However 90% CIs were within acceptable limits as shown in the table below.

Table 28: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Reviewer's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
——— Fasting/Ambien® Fasting	$AUC_{0-\infty}$	1.076	0.986	1.175
	C_{max}	1.049	0.917	1.201

b(4)

Food Effect: Food effect on pharmacokinetic profile of zolpidem after sublingual administration was evaluated using formulation II in this study. Following table represents PK parameters of sublingual zolpidem under fasting and fed conditions.

The mean plasma concentrations of zolpidem were lower for ——— with meal (Treatment A) compared to ——— fasting (Treatment B) and Ambien® fasting (Treatment C). Please refer to figure 8, treatment A for PK profile.

b(4)

The following table shows the PK parameters for [redacted] under fasting and fed conditions.

b(4)

Table 29: Non-Compartmental Pharmacokinetic Parameters mean of all individual values and (SD) of [redacted] under fasting and fed conditions

Pharmacokinetic parameter	OX22 fasting	OX22 with meal
AUC_{0-t} (min*ng/ml)	24295 (10046)	18847 (5645)
AUC_{0-f} (min*ng/ml)	25740 (11027)	20097 (6764)
C_{first} (ng/ml)	8.4 (9.9)	3.9 (2.5)
C_{max} (ng/ml)	106.2 (42.7)	70.5 (18.8)
t_{max} (min)	82 (30-180)	105 (30-240)
$t_{1/2}$ (hr)	2.65 (0.58)	2.39 (0.61)

Food delayed the time to tmax for [redacted] with meal, the median value for tmax was delayed by 28% (105 min). The geometric mean ratio [redacted] with meal [redacted] fasting for AUC0-t was 0.80 (90% CI, 0.73-1.17). Cmax geometric mean ratio was 0.69 (90% CI, 0.60-0.88) when compared to [redacted] fasting (table below).

b(4)

Table 30: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Reviewer's Analysis)

TREATMENT COMPARISONS	PARAMETER	RATIO	LOWER 90% CI	UPPER 90% CI
[redacted] FED/ [redacted] FASTING	$AUC_{0-\infty}$	0.802	0.735	1.175
	C_{MAX}	0.688	0.601	0.876

Discussion: Food also significantly decreased mean AUC and C_{max} of reference listed drug Ambien® by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 84 to 132 minutes). However, effect of food on tmax was larger for Ambien® when compared to [redacted].

b(4)

Conclusions

- [redacted] was bioequivalent to reference Ambien® under fasting conditions. The median tmax's were 82 (range 30-180) minutes for formulation II and 90

b(4)

(range: 30-180) minutes for Ambien® and these differences were not statistically significantly different.

- A statistically significant lower bioavailability was observed for OX22 with meal compared to OX22 fasting and Ambien® fasting with regard to AUC0-t and Cmax.

OX22-008: An open randomized two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia

Study Title	An open randomized two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia
Study number	OX22-008
Study Period	August 30, 2007 to September 17, 2007
Study Director	Caroline Engvall, PhD
Study Design	Single-centre, open, randomized, two-period crossover trial

Study Population: N=18,
Age: 18-45 years
Gender: Healthy Male or Female

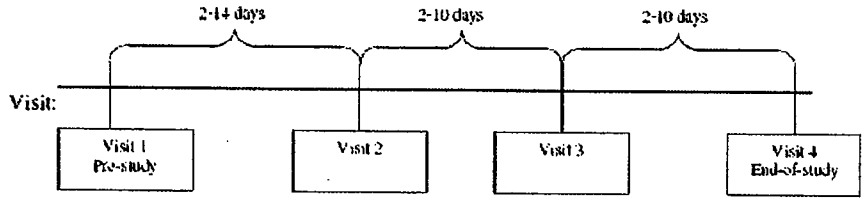
Study Rationale: This study was conducted to establish bridging link between formulation II and to-be-marketed formulation, final commercial product (FCP). Formulation II was shown to be bioequivalent to the RLD Ambien® in study OX22-005. Formulation II is not to-be-marketed or commercial formulation.

Objectives

To assess and compare the PK profile (to prove equivalence) between sublingual **zolpidem, Formulation II** ——— **10 mg,** treatment A) and final commercial product **(FCP) of sublingual zolpidem** ——— **10 mg**, treatment B) both given as single doses after fasting. b(4)

Study Design: This study was conducted as a single-centre, open, randomized, two-period crossover trial to evaluate and compare the bioavailability of two formulations of sublingual zolpidem 10 mg. Treatments were given to the subjects in random order at Visit 2 (Period 1) and 3 (Period 2). Visits 2 and 3 were separated by a wash-out period of 4 days. Overall study design is shown in the figure below.

Figure 1 Overall Study Design



Treatment Groups: Treatment 1 "A": Formulation II 10 mg (Reference)
Treatment 2 "B": Final commercial product (FCP) 10 mg (Test)

Washout period was 4 days

Duration of treatment:
Subjects were administered one dose of OX22, Formulation II (Treatment A) followed by one dose of OX22, FCP (Treatment B) or vice versa, at Visit 2 and Visit 3. There was a wash-out of 4 days between the two treatment visits.

Treatment Instructions
The study medication was placed under the subject's tongue by the study nurse. The zolpidem sublingual tablets were placed directly under the tongue into the deepest part of the oral cavity. It was instructed that the subjects did not move or touch the tablet once it had attached to the mucous membrane. Subjects were also instructed not to swallow the tablet, allowing it to dissolve under the tongue without chewing or sucking. Water was not allowed from one hour before to one hour after dose administration. The time of dose administration commenced when the tablet was placed under the tongue. The subjects were to keep their mouth shut and not deliberately move their tongue for at least 15 minutes.

Method of Assigning Subjects to Treatment Groups (Randomization and Subject Assignment)

This is a randomized study. A treatment randomization list was generated by using the computer program. The subjects were randomized in blocks to sequences AB or BA of treatment periods. The subject received a single oral dose of Treatment A in the first period followed by a single oral dose of Treatment B in the second period or vice versa. Discontinued subjects were replaced with a new subject in order to have eighteen subjects completing the study. Replacement subjects were given a new subject number and received study treatment in the same treatment sequence as the replaced subjects.

Selection of Doses in the Study

Zolpidem dose 10 mg was chosen. This corresponds to the recommended oral dose was 10 mg for adults below the age of 65.

Sampling: Blood samples (7 ml each) for determination of zolpidem in plasma were collected at immediately before (-15-0 minutes) and at 5, 10, 15, 20, 30, 40, 60, 80, 100, 120, 180, 240, 300, 360, 480, and 600 minutes after study drug administration. The accepted deviation for sampling was ± 5% or 15 minutes from the planned time, whichever was the shortest, otherwise it was noted as a protocol deviation. Actual collection times were recorded.

Sample analysis
The concentration of zolpidem was determined using a liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) system. To the plasma samples (500 µl), 50 µl of water and 50 µl of internal standard were b(4)

added, followed by 1.0 ml of ammonium chloride buffer (20 mM, pH 9.3). Liquid-liquid extraction was then performed with 5.0 ml of ethylacetate/dichloromethane 50/50 v/v. The organic phase was removed and evaporated to dryness under a gentle stream of nitrogen at 50 °C. The samples were then reconstituted in 50 µl of aqueous formic acid (0.2%)/methanol 50/50 v/v and transferred to vials for injection into the LC-MS/MS system. The lower limit of quantification was 0.5 ng/ml.

Table 31: Assay performance during the study

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	0.58, 1.50, 10.0, 31.0, 61.0, 204, and 408 ng/mL	Range 1: 0.50, 1.0, 2.1, 3.3, 5.0, 8.4, 15, 39 Range 2: 39, 75, 103, 150, 257, 500 ng/mL
Between Batch Precision (%CV)	**4.0 – 15.1**	**Range 1: 0.34 – 17.8** **Range 2: 0.91 – 6.98**
Linearity	Weighted linear equation ($1/X^2$), Range 1: mean r =0.9998, Range 2: mean r= 0.9990	
Linear Range (ng/mL)	**Range 1: 0.50 – 39 ng/mL** **Range 2: 39 – 500 ng/mL**	
Sensitivity (LLOQ, ng/mL)	0.5 ng/mL	

Pharmacokinetic Measurements:

Area under the plasma concentration time curve from time zero to the last quantifiable sampling point (AUC_{0-t}). Area under the plasma concentration time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), area under the plasma concentration time curve from time 0 to time 30 minutes (AUC_{0-30}), area under the plasma concentration time curve from time 0 to maximal plasma concentration (minutes) [AUC0- t_{max}], time to the first measurable plasma concentration (t_{first}), time to maximal plasma concentration (tmax), terminal elimination half-life (terminal t1/2), first measurable plasma concentration (C_{first}) and maximum plasma concentration (C_{max}) were compared between the treatments.

Statistical methods:

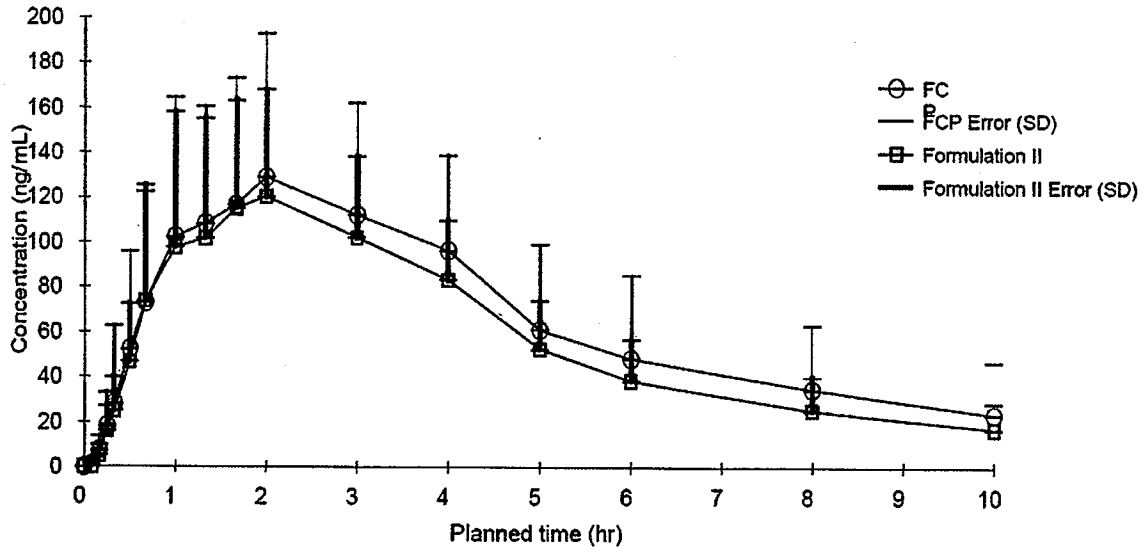
Log transformed parameters for both area under the plasma concentration time curve (AUC) and Cmax were analyzed using an analysis of variance (ANOVA) model with sequence, period and treatment as class variables, and subject (sequence) as a random effect. Differences between treatments were given as 90% confidence intervals (CIs) for the geometric mean ratios, calculated using the adjusted means (LSMEANS) from the analysis of variance (ANOVA) of log-transformed data with subsequent exponential transformation. Equivalence was proven if the 90% CI for the geometric mean ratio B/A for the primary variable AUC0-t (where A was Formulation II and B was FCP) was within the limits 0.80 and 1.25.

Tmax was analyzed using a non-parametric method applied to untransformed data. A Hodges- Lehmann estimate with 90% CI for the median difference between A and B was presented.

RESULTS

Formulation II and FCP of sublingual zolpidem, 10 mg were compared. The geometric mean ratio (90%) CI FCP/Formulation II for the primary variable AUC0-t was 1.10 (1.02-1.19), which was with in the limits 0.80 to 1.25. AUC0-∞ ratio was 1.12 (1.01-1.23). Cmax geometric mean ratio (90% CI) was 1.08 (0.99-1.18). No significant difference was observed for tmax. The median times to first quantifiable concentration (tfirst) as well as tmax were identical for both treatments. Pharmacokinetic profiles for different treatments are shown in the figure below.

Figure 9: Mean (N=18) Plasma Concentration Versus Planned Time Curve After Administration of Formulation II and Final Commercial Product (FCP)



Primary pharmacokinetic parameters used to establish bioequivalence according to sponsor's analysis are presented in the following tables.

Table 32: Treatment Comparisons for FCP versus Formulation II

		90% Confidence Interval	
Pharmacokinetic variable	**Point estimate**	**Lower limit**	**Upper limit**
AUC_{0-t} (hr*ng/mL)[1)]	1.10	1.02	1.19
$AUC_{0-\infty}$ (hr*ng/mL)[1)]	1.12	1.01	1.23
C_{max} (ng/mL)[2)]	1.08	0.99	1.18

Reviewer's re-analysis of the data showed differences in the point estimate ratios and 90% confidence interval (CI) levels for lower boundary and upper boundary. However 90% CIs were within acceptable limits as shown in the table below.

Table 33: Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals (Reviewer's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
FCP/ Formulation II	$AUC_{0-\infty}$	0.896	0.8142	0.9863
	C_{max}	0.926	0.8453	1.0144

Following table summarizes all the pharmacokinetic parameters analyzed in the study.

Table 34: Summary of Pharmacokinetic Variables of Formulation II and FCP

Parameter	Formulation II N = 18		Final Commercial Product (FCP) N = 18	
	Mean	SD	Mean	SD
AUC_{0-t} (ng*h/mL)	579.8	(222.5)	663.3	(310.1)
$AUC_{0-\infty}$ (ng*h/mL)	663.3	(287.3)	786.1	(443.5)
AUC_{0-30} (ng*h/mL)	8.85	(4.67)	10.06	(8.67)
AUC_{0-tmax} (ng*h/mL)	151.0	(82.8)	146.2	(86.1)
C_{max} (ng/mL)	133.40	(47.1)	148.39	(62.5)
C_{first} (ng/mL)	3.16	(3.08)	3.45	(4.29)
	Median	Range	Median	Range
t_{max} (h)	2.00	(1.00 - 4.00)	2.00	(0.33 - 3.00)
t_{first} (h)	0.17	(0.08 - 0.25)	0.17	(0.08 - 0.25)
$t_{1/2}$ (h)	2.89	(2.02 - 4.67)	2.68	(1.76 - 5.56)

Conclusions

- Bioequivalence criteria were met when the pharmacokinetics of FCP and Formulation II of sublingual zolpidem 10 mg, were compared with regard to AUC0-t, AUC0-∞ and Cmax.

- No discernable differences were seen between FCP and Formulation II with respect to tmax.

OX22-006: A double-blind, randomized, two-period crossover study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia.

Study Title	A double-blind, randomized, two-period crossover study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia.
Study number	OX22-006
Study Period	December 2006 to July 2007
Study Director	Corinne Staner, MD
Study Design	Multi-centre, double-blind, double-dummy, randomized, two-period crossover trial

Study Population: N=73,
Age: 18-65 years
Gender: Healthy Male or Female

Objectives

The primary objectives were:

- To evaluate the hypnotic effects on **sleep initiation** by polysomnography (PSG) of a single dose of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia.
  The primary endpoint was
  - Latency to Persistent Sleep (LPS).

  Secondary endpoints were
  - Sleep Onset Latency (SOL) and
  - Latency to Stage 1 (ST1L).
- To evaluate the hypnotic effects on **sleep continuity** by PSG of a single dose of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. The following PSG variables were tested.
  - Total Sleep Time (TST),
  - Number and duration of awakenings after sleep onset (WASO).

The secondary objectives were:

- To evaluate by PSG other visually scored night sleep variables, other latency variables, sleep continuity and sleep architecture, the patient's subjective assessment of sleep and next day residual effects of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia.
- To assess tolerability and safety of the study treatments.

Study Design: The screening visit was divided into one initial day, followed by two consecutive screening nights. For eligible patients, the screening visit was followed by two assessment periods of three days and two nights each. In the evening of Day 1, using the

double-dummy method, patients were administered a single dose of OX22 or Ambien® and the placebo to the corresponding treatment. The order in which patients received OX22 and Ambien® was randomized. The PSG recordings were initiated immediately after product administration. No food was allowed from 3 h before product administration to the end of the PSG recording period (in the morning of Day 2). The patients remained at the study center until the afternoon of Day 2. The investigator authorized them to leave the center after a review of the safety results. The end of study visit (one day) took place between 7 and 14 days after the end of the second assessment period.

Test Product: OX22 (sublingual zolpidem) was administered as single sublingual tablet of 10 mg.
Reference Product: Ambien® (overencapsulated immediate-release zolpidem tablet) was administered as single oral capsule of 10 mg.

Duration of treatment:
The patients received one single dose of OX22 or Ambien® and one single dose of the matching placebo of the corresponding drug on the evening of Day 1 in each treatment period, according to a randomized schedule. A 7-14 day wash-out period was included in between treatment periods. Each study treatment (OX22 and Ambien®) was administered once during the study.

Criteria for evaluation:

A standard PSG consists of the simultaneous recording of four electrophysiological signals:

- Cerebral activity recorded via the electroencephalogram (EEG)
- Ocular movement recorded via the electro-oculograms (EOG)
- Muscular tone recorded via the sub chin electromyograms (EMG)
- Cardiac activity recorded via the electrocardiogram (ECG)

Recordings of sleep were scored by sleep technicians. The different visual sleep parameters were derived from the visual scoring of the recordings using the Hypnos software. Two kinds of sleep parameters were derived from the visual analysis of sleep:

- Sleep continuity parameters comprised both sleep initiation and sleep maintenance variables.
- Sleep architecture parameters comprised stages distribution variables documenting duration and proportion of the different sleep stages and sleep profile variables that provided an outline on the time course of the different sleep stages during the recording period.

The **primary pharmacodynamic endpoints** consisted of sleep parameters measured by PSG in order to assess both the hypnotic effects on sleep initiation and the hypnotic effects on sleep continuity (maintenance) of OX22 versus Ambien®.

The primary sleep initiation endpoint was:

- Latency to Persistent Sleep (LPS)

The secondary sleep initiation endpoints were:

- Sleep Onset Latency (SOL)

- Latency to Stage 1 (ST1L)

The sleep continuity (maintenance) endpoints were:

- Total Sleep Time (TST)
- Number and duration of awakenings after sleep onset (WASO)

The following **secondary pharmacodynamic endpoints** were assessed:

- Other visually scored night sleep variables, such as sleep continuity (maintenance), sleep architecture and sleep profile variables (from PSG measurements)
- Subjective assessment of sleep: Leeds Sleep Evaluation Questionnaire (LSEQ). The LSEQ was used to monitor subjectively perceived changes in sleep.
- Next day residual effects: Bond and Lader Visual Analogue Scale (VAS), Digit Symbol Substitution Test (DSST) and Leeds psychomotor tests.

The following safety variables were assessed:

- Adverse events
- ECG
- Vital signs
- Laboratory results (biochemistry, hematology and urinalysis)
- Physical examinations

Statistical methods:

Pharmacodynamic analyses:
PSG variables for the two treatments were compared in a two-period crossover analysis using an ANOVA model with study center, sequence, patient, period and treatment as class variables. Differences between treatments were estimated and tested within the statistical model. Exploratory analyses of the secondary variables were carried out and tabulated by treatment as numbers (n), means, standard deviations and min- and max-values. All evaluable patients (per protocol set) were included in the pharmacodynamic analyses.

Safety analyses:
Safety was assessed for all randomized patients who had taken at least one dose of study medication (all patients in this study). Vital signs, ECG, laboratory results and physical examination were tabulated by parameters, investigational medicinal product (IMP) and time for all patients. Adverse events were coded and classified according to their preferred term and then tabulated according to their intensity and their relationship to the study treatments.

RESULTS

Three patients were excluded from the per protocol set. Patients No. 322-005 and 703-002 were excluded because the start time of the PSG recording was not immediately after test product administration. Patient No. 701-003 was excluded since she discontinued the study due to SAEs (pregnancy and miscarriage).

Data Sets Analyzed

Randomized set n=73			
Pooled center 1 n=19	Pooled center 2 n=19	Pooled center 3 n=14	Pooled center 4 n=21

Polysomnography sleep parameter results are provided in the following table.

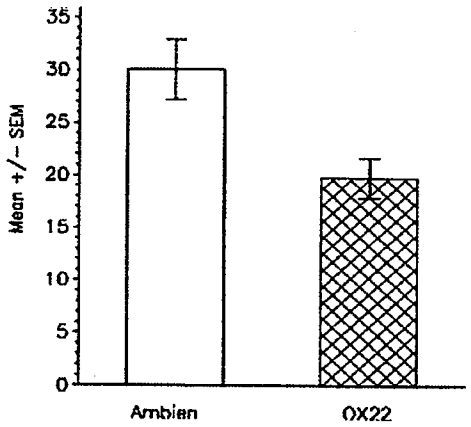
Table 35: Polysomnography Sleep Parameter Results

Variables*	Baseline	Zolpidem tartarate sublingual tablets10 mg (min)	Ambien® 10 mg (min)	Treatment Differences	
				Estimates (± SD) (minutes)	p-value
Sleep Initiation					
LPS	84.54 ± 40.35	19.76 ± 15.55	30.06 ± 23.48	-10.2823 ± 2.98	0.0010
ST1-L	72.30 ± 39.32	17.66 ± 13.37	26.31 ± 22.72	-8.6307 ± 2.80	0.0030
SOL	61.07 ± 34.64	13.94 ± 12.67	21.35 ± 20.30	-7.4273 ± 2.24	0.0047
Sleep Maintenance (Continuity)					Confidence Intervals (Minutes)
TST	324.29± 46.52	432.06 ± 29.30	424.72 ± 34.42	7.2243 ± 3.60	(0.0213, 14.4272)
WASO	84.08 ± 36.16	30.87 ± 27.79	29.82 ± 26.80	1.1250 ± 3.08	(-5.0293, 7.2793)

*The variables are expressed in minutes (mean ±SD).

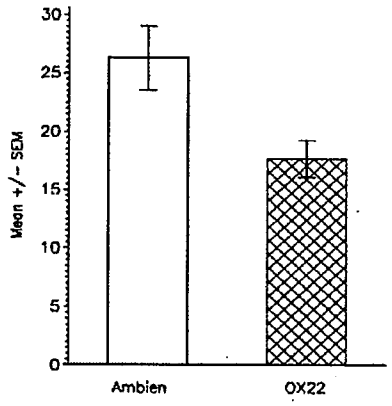
Following bar charts also indicate the results of PSG.
Sleep Initiation Parameters: latency to persistent sleep (LPS), sleep onset latency (SOL) and latency to stage 1 (ST1L).

Bar charts of mean (± SEM) observed values for latency to persistent sleep (LPS)

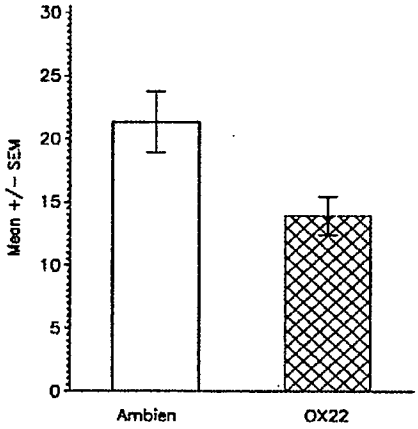


For the primary sleep initiation endpoint, the ANOVA revealed a significant treatment (p =0.001) effect. Compared to Ambien®, OX22 significantly shortened the LPS with an estimate of about 10 min and a 95 % CI ranging from -4.3 min to -16.2 min.

Bar charts of mean (± SEM) observed values for sleep onset latency (SOL)



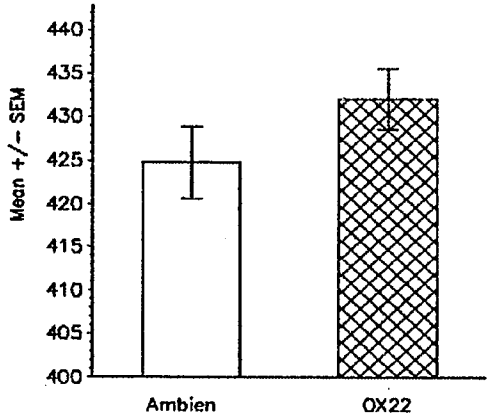
Bar charts of mean (± SEM) observed values for latency to stage 1 (ST1L)



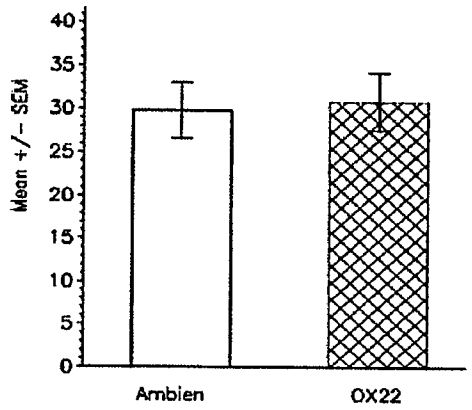
For the two secondary sleep initiation endpoints (SOL and ST1L) a significant ($p < 0.01$) treatment effect was found. Compared to Ambien®, OX22 significantly shortened SOL and ST1L. Estimate was about 9 min (95% CI: - 3.0 to –14.2 min) for SOL and about 7 min (95% CI: - 2.4 to -12.5 min) for ST1L.

Sleep Continuity (maintenance) Parameters: total sleep time (TST) and duration of wake after sleep onset (WASO).

Bar charts of mean (± SEM) observed values for total sleep time (TST)



Bar charts of mean (± SEM) observed values for duration of wake after sleep onset (WASO)



For the sleep continuity (maintenance) parameters (TST and WASO), an analysis of treatment differences showed that OX22 increased TST more than Ambien®, with an estimated treatment difference of about 7 min and a 95% CI ranging from 0.02 to 14.4 min.

The non-inferiority limit was obtained for TST but not for WASO.
Next day subjective assessment of residual effects

- Bond and Lader Visual Analogue Scale (VAS) - alertness, contentedness and calmness
- Digit Symbol Substitution Test (DSST) - attention and concentration
- Leeds psychomotor tests (MCRT and CFFT)- attention abilities and vigilance

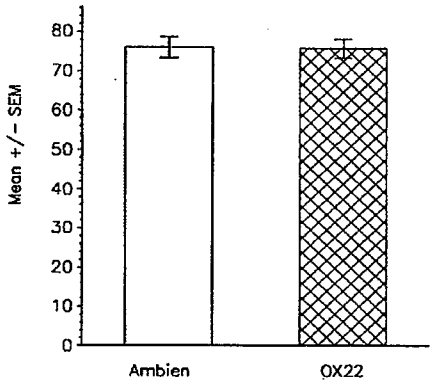
Next-Day Residual Effects: Digit Symbol Substitution Test (DSST) and Visual Analogue Scales (VAS).

Results of the next day residual effects indicated that there were no differences between OX22 and Ambien®.

Digit Symbol Substitution Test (DSST)

The DSST consisted of matching digits to symbols according to a defined code. The parameter derived from this test was the number of correct answers recorded in 180 seconds. A decrease of the score meant a decrease in concentration capacities and a decrease in speed of information processing.

Digital substitution test – Barcharts of mean (+/ – SEM) – Observed values per protocol set, P-value 0.5885



No significant treatment effect could be demonstrated by DSST.

Visual Analogue Scales (VAS – Bond and Lader)

Three parameters were taken into account in the analyses of the VAS (Bond and Lader):

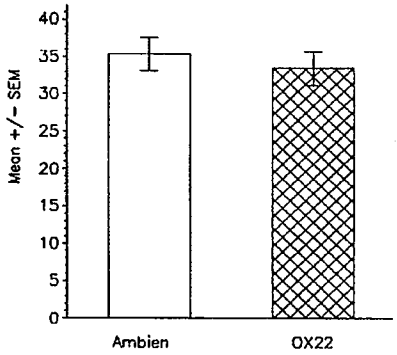
- alertness
- contentedness
- calmness

The alertness scale was an index of subjective vigilance feeling, the contentedness scale indicated the subjective satisfaction feeling and the calmness scale was an index of subjective quietness feeling. The scores were expressed in millimeters and an increase in the score meant a decrease in the intensity of the corresponding feeling and vice versa.

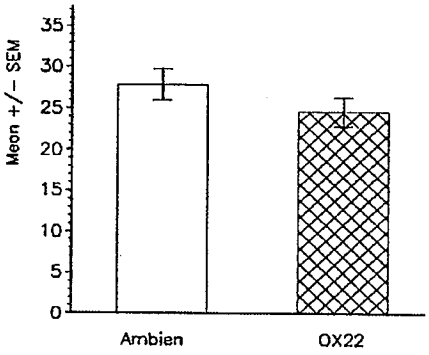
ANOVA results indicate that there was no treatment effect for any of the three parameters (P values 0.382, 0.052 and 0.455 respectively).

Bond and Lader VAS – Barcharts of mean (+/ – SEM) – Observed values on day 2- Per protocol set

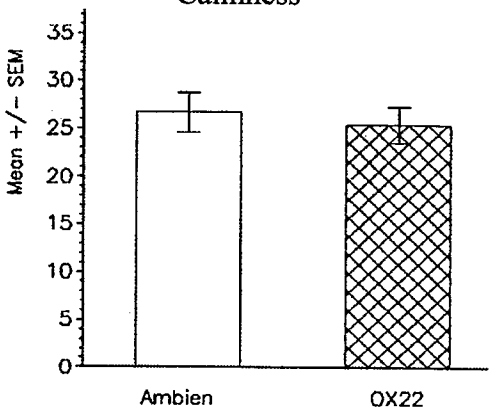
Alertness



Contentedness



Calmness



Presubmission Regulatory Activity Related to Submission

b(4)

Discussion: Ambien® has been shown to decrease sleep latency for up to 35 days in controlled clinical trials, according to indications of Ambien® label. The Study OX22-006 is a single-dose study evaluating pharmacodynamic (PSG) parameters.

b(4)

Overall Conclusions

- Compared to Ambien®, ——— **significantly shortened** the primary end points, sleep initiation (LPS) and two secondary sleep initiation endpoints (SOL and **ST1L). However, for** —— **the two other** endpoints of the primary objectives (wake after sleep onset and total sleep time), non-inferiority limit was not achieved. b(4)

- Sleep subjective assessment of residual effect parameters, digital symbol substitution test, visual analogue scales, Leeds psychomotor test-multiple choice reaction time and critical flicker fusion test indicated no significant treatment effect.

B OCP Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21997	Brand Name	b(4)
OCPB Division (I, II, III)	DCP-1	Generic Name	Zolpidem Tartrate
Medical Division	HFD-120	Drug Class	Imidazole Pyridine Sedative/Hypnotic
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Insomnia
OCPB Team Leader	Veneeta Tandon	Dosage Form	Sublingual Tablet
Date of Submission	05/14/2008	Dosing Regimen	10 mg Before Bedtime
Estimated Due Date of OCPB Review	01/24/2009	Route of Administration	Oral
PDUFA Due Date	3/14/2009	Sponsor	Orexo AB
Division Due Date	2/21/2009	Priority Classification	S

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of ——— (previously referred to as OX 22, ———) available in 5 mg and 10 mg strength tablets for sublingual administration. OX22 a sublingual tablet of zolpidem tartrate currently marketed under trade name of Ambien® in the form of oral tablets. The pharmaceutical development ——— was designed to show bioequivalence between this new dosage form of zolpidem tartrate and marketed Ambien® in terms of Cmax and AUC. b(4)

Seven clinical studies were conducted to support the application (Appendix 3: Tabular listing of clinical studies). Three different formulations were used during the development ——— . Difference in the formulations is presented in Appendix 1. The following studies supporting the proposed indication for treatment of short-term insomnia in adults comprise 3 comparative, single-dose pharmacokinetic (PK)/bioequivalence (BE) bridging studies in 66 (per protocol) healthy adult subjects, 18- 40 years of age, including:

1) OX22-004, Formulation I versus Formulation II (10 mg ———)
2) OX22-005, Formulation II (10 mg OX22) versus 10 mg Ambien® and
3) OX22-008, Formulation II versus the Final Commercial Product (10 mg ———) b(4)

Establishment of bioequivalence between Formulation II OX22 and Ambien® and effect of food intake on the pharmacokinetics of sublingually administered zolpidem was made in OX22-005. Comparative bioequivalence studies were dealt with Formulations I and II and the Final Commercial Product were made in OX22-004 and OX22- 008, respectively.

The relationship between the pharmacokinetic profile and the sleep laboratory polysomnography/pharmacodynamic (PSG /PD) effects of 10 mg Formulation II OX22 and Ambien® was made by comparing results of the OX22-005 and OX22-006 studies. OX22-001 examined the pharmacokinetic dose proportionality and linearity of single doses of 5 mg and 10 mg OX22 (Formulation I) when administered sublingually. OX22-002 examined the hypnotic effect and safety of single doses of **5 mg and 10 mg** ——— **(Formulation I).** ——— **formulations** containing 5mg and 10 mg zolpidem tartrate are proportionally similar. b(4)

Note: OX22-001 and OX22-002 compared 10 mg of the Stilnoct®, (oral zolpidem, Sanofi- Aventis , **Europe) with 5 and 10 mg dosage form of** ———.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	2		
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	-	-	
multiple dose:				
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	-	**Study OX22-001: Dose linearity (5 and 10 mg) and Relative BA study (reference treatment was Stilnoct®)**
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	X	1	-	**Study OX22-006: PD part only**
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	

Relative bioavailability -	-	-		**Study OX22-001**
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		**3**		**Studies OX22-004, OX22-005, OX22-008**
replicate design; single / multi dose:				
Food-drug interaction studies:		-		**Study OX22-005**
Dissolution:	-	-	-	
(IVIVC):				
Bio-waiver request based on BCS	-	-	-	
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References				
Total Number of Studies		**4 + 1 PK/PD+ 2 Assay studies**		

(c) Filability and QBR comments

	"X" if yes	
Application filable?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	-	
QBR questions (key issues to be considered)		1) Is BE shown between sublingual tablets OX22 and reference Ambien® tablets 2) Is final marketed product bioequivalent to formulation II used in pivotal BE study? 3) Is there a dose proportionality between 5 and 10 mg sublingual tablets?

Other comments or information not included above	Request for DSI inspections: **1) Pivotal BE study** **Study OX22-005:** An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for treatment of short-term insomnia. **2) Formulation bridging study** **Study OX22-008:** An open randomized, two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia (tobe marketed vs formulation II used in pivotal BE study) **Study samples from OX22-005 and OX22-008 were analyzed at Analytical Laboratory:**
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

b(4)

CC: NDA 21997

HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Veneeta Tandon, Ramana Uppoor, Mehul Mehta)

Appendix 1: Composition of different formulations used in the clinical studies.

Table 1 Formulations of Zolpidem tartrate sublingual tablets used in clinical and nonclinical development programs

Components	Function	Formulation I (mg)	Formulation II (mg)	Final Commercial Product (mg)
Zolpidem tartrate	Drug substance	5.00/10.0		
[redacted]				
Zolpidem tartrate, [redacted]	Drug substance	-	10.0	10.0
[redacted]				
Mannitol [redacted]				
[redacted]				
Silicon dioxide, colloidal				
Silicified microcrystalline cellulose				
Croscarmellose sodium				
[redacted]				
[redacted]				
Saccharin sodium				
[redacted]				
Magnesium stearate				
Total weight		**80.0 mg**	**105 mg**	**130 mg**
Formulation(s) used for clinical programs				
		OX22-001		
		OX22-002	59259[1]	
		OX22-004[2]	OX22-004	
			OX22-005	
			OX22-006	
				OX22-007
			OX22-008	OX22-008

b(4)

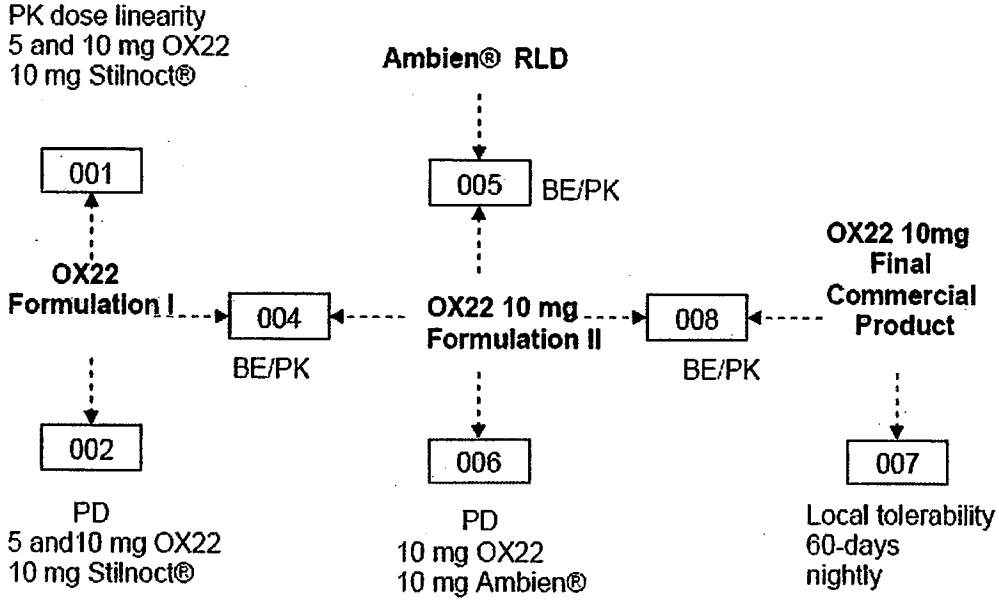
[1] Nonclinical Study, Oral irritation test in the Syrian Hamster
[2] Only Zolpidem tartrate sublingual tablet 10 mg was studied.

Table 6: Final Commercial Product (FCP) - Composition of Zolpidem tartrate sublingual tablets 5 and 10 mg

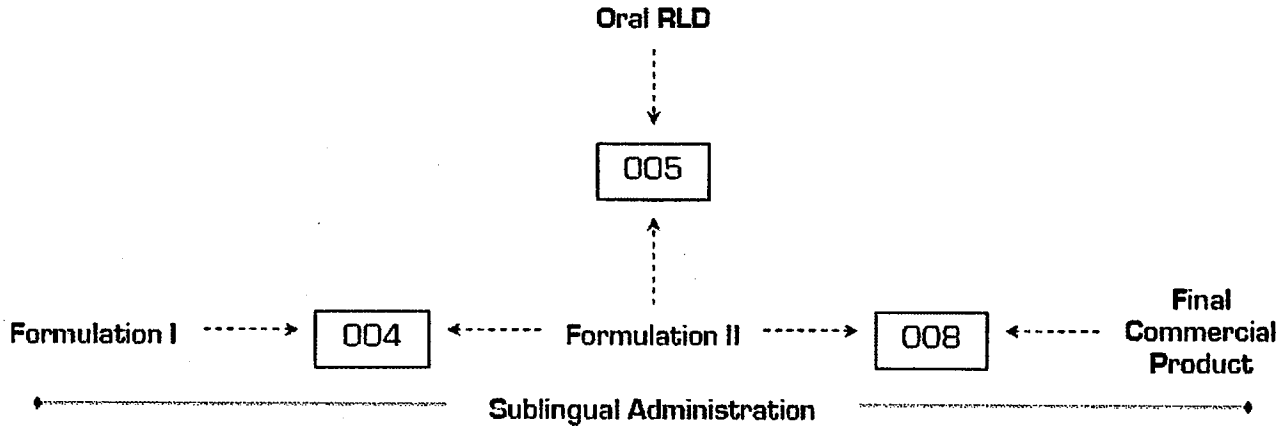
Components	Each 5 mg tablet contains (mg)	Each 10 mg tablet contains (mg)	Function	Reference to quality standard
Zolpidem tartrate.	5.00	10.0	Drug substance	Ph. Eur.
Mannitol				USP, Ph. Eur. b(4)
Silicified microcrystalline cellulose[3]				USP, Ph. Eur.
Silicon dioxide, colloidal				USP, Ph. Eur.
Croscarmellose sodium				USP, Ph. Eur.
Saccharin sodium				USP, Ph. Eur.
Magnesium stearate				USP, Ph. Eur.
Tablet weight	**120 mg**	**130 mg**		

Appendix 2: Schematic diagrams representing bridging studies

Figure 1: OX22 Clinical Development



Stilnoct® Oral zolpidem, Sanofi-Aventis, EU



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Appendix 3: Tabular listing of clinical studies.

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
Healthy Subjects – Single Doses						
OX22-001 An open randomized, three-period crossover, single-centre study to evaluate the pharmacokinetic profile of sublingual zolpidem 5 mg and 10 mg, and of oral zolpidem (Stilnoct®) 10 mg	Healthy male or female volunteer subjects. 18-40 years 8 males 10 females	1) To compare bioavailability[3] of OX22 (10 mg) and Stilnoct®[4] (10 mg) 2) To compare bioavailability with regard to dose proportionality between OX22 (5 and 10 mg), to prove linearity.	18 subjects planned/ 18 randomized/ 18 per protocol/ 18 safety analyses 18 PK analyses 18 Sedation scores (VAS) 5 mg and 10 mg OX22 10 mg Stilnoct®	Formulation I (5 mg and 10 mg sublingual tablets OX22)[3]	Bo-Lennart Johansson, M.D.	Filed in original NDA 21-997 b(4)

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
OX22-002 An open randomized, three-period crossover, single-centre study to evaluate the hypnotic efficacy and safety of sublingual zolpidem 5 mg and 10 mg compared to oral zolpidem (Stilnoct®) 10 mg in healthy volunteers	Healthy male or female volunteer subjects. 18-40 years 4 males 17 females	Primary: - To evaluate the efficacy of single doses of sublingual zolpidem (5 and 10 mg)[4] versus oral zolpidem (10 mg)[4] in healthy volunteers, in a post-nap model, with regard to latency to persistent sleep (LPS), a polysomnographic (PSG)-derived variable that assesses objective sleep latency. Secondary: - To evaluate (by PSG) the effects of single doses of sublingual zolpidem (5 and 10 mg) versus oral zolpidem (10 mg) in healthy volunteers on other sleep latency variables, on sleep continuity and sleep architecture variables, on sleep EEG power spectra as well as on the patient's subjective assessment of sleep. - To evaluate the next day residual effects and the safety of single doses of sublingual zolpidem OX22 (5 and 10 mg) versus oral zolpidem (10 mg) in healthy volunteers.	18 planned/ 21 randomized/ 18 per protocol/ 21 safety analyses 18 PSG analyses 5 mg and 10 mg OX22 10 mg Stilnoct®	Formulation I (5 mg and 10 mg sublingual tablets OX22)	Jean-Paul Macher, M.D. ———	Filed in original NDA 21-997 b(4)

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
OX22-004 An open randomized, two-period crossover, study to assess the bioavailability of sublingual zolpidem for the treatment of short-term insomnia	Healthy male or female volunteer subjects, fasting. 18-40 years 8 males 4 females	Bioavailability[3] of an optimized pharmacological composition of sublingual zolpidem (A)[4] with a previously developed sublingual zolpidem composition (B), given as single doses of 10 mg.	12 subjects planned/ 12 randomized/ 12 per protocol/ 12 safety analyses 12 PK analyses 10 mg (Formulation I) OX22 10 mg (Formulation II) OX22.	Formulation II (10 mg sublingual tablets OX22) Formulation I (10 mg sublingual tablets OX22)	Pierre Lafolie, M.D.	Filed in original NDA 21-997

b(4)

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
OX22-005 An open randomized three-period crossover study to evaluate the pharmacokinetic profile of sublingual zolpidem for the treatment of short-term insomnia	Healthy male or female volunteer subjects. 18-40 years 12 males 6 females	Primary objectives: To assess and compare the pharmacokinetic profile (to prove equivalence[3]) of sublingual zolpidem (Sublinox™ 10 mg[4], treatment B) and oral zolpidem (Ambien® 10 mg, treatment C, reference) both given as a single doses after fasting. To assess and compare the pharmacokinetic profile (to test for a difference) of sublingual zolpidem (Sublinox™ 10 mg) given as single doses immediately after a meal (treatment A) or after fasting (treatment B, reference). To assess and compare the pharmacokinetic profile (to test for a difference) of sublingual zolpidem (Sublinox™ 10 mg, treatment A) given as a single dose immediately after meal, and oral zolpidem (Ambien® 10 mg, treatment C, reference) given as single dose after fasting. Secondary objective: To assess tolerability and safety	18 subjects planned/ 18 randomized/ 18 per protocol/ 18 safety analyses 18 PK analyses 10 mg OX22 with meal, 10 mg OX22 fasting 10 mg Ambien® fasting	Formulation II (10 mg sublingual tablets OX22)	Pierre Lafolie, M.D.	IND amendment SN 0012, Nov. 13, 2007 b(4)

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
OX22-008 An open randomized, two-period crossover study to assess the bioavailability of two different formulations of sublingual zolpidem for the treatment of short-term insomnia.	Healthy volunteers, males or females, between 18 and 45 years of age, fasting. 7 males 12 females	Primary objective: To assess and compare the pharmacokinetic profile (to prove equivalence[3]) between sublingual zolpidem, Formulation II (Sublinox™ 10 mg[4], treatment A) and final commercial formulation of sublingual zolpidem (Sublinox™ 10 mg, treatment B) both given as single doses after fasting. Secondary objectives: To assess tolerability and safety.	18 subjects planned/ 19 randomized/ 18 per protocol / 19 safety analyses 18 PK analyses 10 mg OX22	Formulation II (10 mg Sublingual tablets OX22) Final Commercial Product (10 mg Sublingual tablets OX22)	Magnus Wickström, M.D.	IND amendment SN 0013, Nov. 16, 2007 b(4)

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Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
Patients with Insomnia – Single Doses						
OX22-006 A double-blind, randomized, two-period cross-over study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia	Male and female patients between 18 and 65* years meeting the DSM-IV criteria for primary insomnia and presenting symptoms for at least 3 months in duration 31 males 42 females *Enrolled patients were less than 65 years of age.	Primary objectives: - To evaluate the hypnotic effects on sleep initiation by PSG of a single dose of sublingual zolpidem[4] versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. The primary endpoint was Latency to persistent Sleep (LPS) (to test for superiority). Secondary endpoints were Sleep Onset Latency (SOL) and Latency to Stage 1 (ST1L). - To evaluate the hypnotic effects on sleep continuity by PSG of a single dose of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. The following PSG were tested for "at least as good as": Total Sleep Time (TST), Number and duration of awakenings after sleep onset (WASO). Secondary objectives: - To evaluate by PSG other visually scored night sleep variables, other latency variables, sleep continuity and sleep architecture, the patient's' subjective assessment of sleep and next day residual effects of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. - To assess tolerability and safety of the study treatments.	72 patients planned/ 73 randomized/ 70 per protocol/ 73 safety analyses 70 PSG analyses 10 mg OX22 and matching placebo 10 mg Ambien® and matching placebo	Formulation II (10 mg sublingual tablets OX22)	Corinne Staner, M.D[3]., coordinating investigator for 2 sites in France.	IND amendment SN 0012, Nov. 13, 2007 b(4)

Title / Description	Population / Age	Objectives/Design	No. of Subjects/Patients and Doses Evaluated	Formulation of OX22[1]	PI & Locations[2]	Status
Patients with Insomnia – Multiple Doses						
OX22-007 An open labeled clinical trial evaluating the local tolerance and safety of sublingual zolpidem in insomnia patients	Patients (male and female), aged 18-64 (inclusive), suffering from chronic insomnia (difficulty initiating or maintaining sleep or non-restorative sleep lasting for at least 1 month prior to the pre-study visit) 20 males 40 females	Primary objectives: To evaluate the local tolerance in the sublingual mucosa after daily treatment with OX22 (sublingual zolpidem 10 mg)[4] for 60 days in chronic insomnia patients. Secondary objectives: - To evaluate the patient's subjective assessment of treatment with OX22. - To assess tolerability and safety	60 patients planned/ 60 enrolled/ 53 per protocol/ 60 safety analyses 10 mg OX22	Final Commercial Product (10 mg sublingual tablets OX22)	Brian C. Pogue, M.D..	IND amendment SN 0013, Nov. 16, 2007 b(4)

Footnotes:

[1]Refer to Table 9.2.1 for composition of OX22 formulations used in the clinical development program. *There was no study designated as OX22-003.*

[2]Other Primary Investigators: France (Jose Haba-Rubio, M.D); Belgium (Ilse De Volder, M.D., Stephane Noel, M.D.); Russia (Elena Alekseeva, M.D., Elmira Sagutdinova, M.D., Irina Vlasova, M.D., Olga Chizhova, M.D., and Mikhail Smirnov, M.D.)

[3]Determination of whether "bioequivalence" criteria have been met.

[4]OX22 = zolpidem sublingual tablets = Sublinox™ (Orexo AB; early terminology no longer applicable); Ambien® = zolpidem oral tablets (Sanofi-Aventis, US); Stilnoct® = zolpidem oral tablets (Sanofi-Aventis, Europe)

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/s/

Jagan Parepally
2/12/2009 12:23:28 PM
PHARMACOLOGIST

Veneeta Tandon
2/12/2009 12:56:54 PM
BIOPHARMACEUTICS