CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21997
Submission Number	
Submission Code	
Letter Date	
Stamp Date	
PDUFA Goal Date	March 14 2009
Reviewer Name	Suhail Kasim, MD
Review Completion Date	3/09/09
Established Name	Zolpidem Tartrate Tablets
(Proposed) Trade Name	Edluar
Therapeutic Class	Hypnotic
Applicant	Orexo AB
Priority Designation	S
Formulation	Sublingual tablet
Dosing Regimen	10 mg once daily
Indication	Short-term Insomnia
Intended Population	Adult patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that this product be approved for use in the adult population for the treatment of short term insomnia. There are no significant clinical safety concerns that would preclude approval. The sponsor has met the Agency's requirements for successful approval of this 505 (b)(2) application by showing bioequivalence of the sublingual formulation of zolpidem to Ambien, and by providing adequate CMC related data.

1.2 Recommendations for Postmarketing Risk Management Activities

There is no recommended risk management activity for this product.

1.3 Recommendations for other Post Marketing Study Commitments

There are no post-marketing study commitments for this product.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed trade name for sublingual zolpidem is still pending approval. It is an imidazopyridine class hypnotic with an affinity for the benzodiazepine (BZ_1) receptor of $GABA_A$. It's chemical name is N,N,6-Trimethyl-2-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-acetamide, (2R,3R)]-2,3-dihydroxybutanedioate (2:1).

Each Zolpidem tartrate sublingual tablet includes the following inactive ingredients: mannitol, colloidal silicon dioxide, silicified microcrystalline cellulose, croscarmellose sodium, saccharin sodium, and magnesium stearate.

Orexo AB proposes using Zolpidem tartrate sublingual tablets for the short-term treatment of insomnia in adults characterized by difficulties with sleep initiation. The proposed adult dose is 10 mg sublingual once daily immediately before bedtime and 5mg sublingual once daily immediately before bedtime in elderly/debilitated patients or patients with hepatic impairment.

Via email communication, the FDA required clarification on 02/10/2007 whether the Sponsor was [redacted] using results from the efficacy trial OX22-006. The Sponsor responded [redacted] that they would only describe the pharmacodynamic profile in the Prescribing Information. [redacted] b(4)

On 04/05/2007, the FDA had a Type C guidance meeting with the Sponsor. The CSS division concluded that the Sponsor did not have to do additional abuse liability studies or interaction studies with alcohol if there were no significant differences in T_{max} between Ambien and Zolpidem tartrate sublingual tablets (but if there was a difference eg., shorter T_{max}, the Sponsor would have to include in the label greater impairment and abuse potential). This would be a matter of review. However, the FDA reiterated that the label should clearly reflect the findings from the pharmacodynamic studies in line with the request to all manufacturers of sedative-hypnotic products, to strengthen their product labeling to include stronger language concerning potential risks.

On 01/16/2008, there was a pre-NDA meeting for application NDA 21-997/IND 69,200 included discussions about obtaining 3 year product exclusivity, relevant pharmacokinetic and pharmacodynamic studies etc. The FDA commented that the Sponsor would be able to rely on findings of safety and effectiveness from RLD (Ambien) label by doing adequate bridging studies, from published literature reports, as well as data from the OX22 clinical program in support of the proposed 505(b)(2) application. The Sponsor would submit a detailed ISS for all clinical studies performed and only summaries of key studies in place of ISE since it was a 505 (b)(2) application.

The application was filed in accordance with 21 CFR 314.101(a) on 07/10/2008. The review classification for this application was Standard and the user fee goal date was 03/14/2009. The Sponsor submitted updated RLD label on 06/11/2008.

2.6 Other Relevant Background Information

There is no other relevant background information for this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

We selected two sites for inspection in relation to this submission, both of which were selected from the study protocol OX22-006. Study site 703, headed by Dr. Vlasova at City Clinical Hospital, Moscow, Russia was selected because the most number of patients were enrolled and

2.2 Available Treatments for Short-Term Insomnia

For the treatment of short term insomnia in adults, currently FDA approved sedative-hypnotics include Ambien (Zolpidem), Sonata (Zaleplon), Halcion (Triazolam), Prosom (Estazolam), Restoril (Temazepam) and Lunesta (Eszopiclone). Ramelteon, a melatonin receptor agonist, is indicated for sleep-onset difficulties. Other treatments for chronic insomnia include Benzodiazepine class of drugs, tricyclic anti-depressants, anti-histamines, and some OTC products.

There are currently no sedative-hypnotics which have been approved for use in the pediatric population.

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is currently being marketed by Sanofi-Aventis US as Ambien® and as Ambien CR®, and is available as generic zolpidem tartrate 5 and 10 mg tablets.

2.4 Important Safety Issues With Non-Benzodiazepine Sedative-Hypnotic Drugs

In March, 2007 the FDA requested label changes for all sleep disorder drug products to include stronger language about potential adverse events including anaphylaxis and complex sleep-related behaviors (sleep-driving, making phone calls, preparing and eating food during sleep, or having sex). In addition to the labeling changes, Patient Medication Guides had to be distributed when medications were dispensed. The safety concerns associated with some of the hypnotics have been explained below after literature review and information already available from the Ambien® label.

Next-day residual effects (Hangover): Elderly subjects treated with Ambien experienced a decrease in performance when compared to placebo. In non-elderly patients with insomnia there was no evidence of next-day residual effects. Next-day residual deficits occur most frequently with long-acting benzodiazepines (characterized by a half-life > 24 hours and pharmacologically active metabolites), although they are also observed following the administration of intermediate-acting agents (characterized by a half-life of 4–24 hours and few active metabolites).

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia following discontinuation of Ambien. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg. Withdrawal symptoms occur more rapidly and more frequently with the short acting benzodiazepines (characterized by a half-life of < 4 hours) compared with the longer-acting benzodiazepines. Rebound insomnia was observed with Eszopiclone 2 mg on the first night after discontinuation. No significant evidence of rebound insomnia or serious withdrawal reactions has been documented with Zaleplon after 4 weeks of treatment.

Memory impairment: Subjects who received more than Ambien 10 mg, experienced difficulty with next-morning recall of information during peak drug effect (90 minutes post-dose) in one study and there was subjective evidence of anterograde amnesia occurring when more than Ambien 10 mg was given. The ultra-short half-life of Zaleplon contributes to the low propensity toward next-day effects on memory in healthy individuals and in those with insomnia.

Effects on sleep stages: In studies that measured the percentage of sleep time spent in each sleep stage, Ambien has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

Potential for abuse/Tolerance: Ambien showed additive effects when taken with alcohol and there is reasonable warning to believe that its additive effects can be seen when taken with other CNS depressants. Eszopiclone was assessed over 6 and 12 months, and tolerance was not observed. Zaleplon has a favorable safety profile and is well tolerated.

Dependence: Dependence on Eszopiclone has not been reported, although it is classified as a schedule IV medication along with other hypnotics by federal regulation, and no evidence of serious withdrawal syndrome was reported.

Behavioral Changes: Complex-behaviors such as sleep-driving, preparing and eating food, making phone calls, or having sex have been seen in patients who are not fully awake after taking sedative-hypnotics. There is amnesia related to these events. Some patients have exhibited bizarre behavior, aggressiveness and extroversion out of character, agitation and depersonalization including visual and auditory hallucinations, which was also seen in pediatric patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor had pre-IND discussions on 11/16/2004 with the Division of Anesthetic, Critical Care, and Addiction Drug Products, ODE II, FDA in preparation to file new drug application (NDA) under section 505 (b)(2). Discussion included details regarding conducting studies necessary to establish safety, bioavailability and efficacy through IND 69,200. The IND was transferred to the Neuropharmacological Division, ODE I, FDA on 04/26/2005.

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 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.

reported an increased frequency of adverse events. Study site 331, headed by Dr. Staner at FORENAP Pharma, Rouffach, France was selected because it enrolled the second highest number of patient's (46.5% of the patients in study OX22-006) with a contribution to the overall treatment affect. There was also a disparity between screening and recruitment of patients at this site.

DSI inspection of Dr. Staner found regulatory violations concerning pregnancy testing and lack of source documentation for a secondary endpoint. However, the data from both clinical sites and from the CRO appeared acceptable in support of the application for the proposed indication.

3.2 Compliance with Good Clinical Practices

DSI inspection report includes the inspected sites have been in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure information (FORM FDA 3454) was submitted by the Sponsor from the principal and sub-investigator's for studies OX22-001, OX22-004, OX22-005, OX22-007, and OX22-008.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to FDA CMC review.

4.2 Nonclinical Pharmacology/Toxicology

As a 505(b)(2), pharmacology/toxicology is based largely on previous FDA nonclinical findings for zolpidem. Additional non-clinical local toxicity studies of the oral surface were deemed not necessary since there were no significant adverse events due to the brief contact of the sublingual tablet with the oral surface, and little indication of meaningful drug absorption through the oral surface.

4.3 Clinical Pharmacology

4.3.1 Pharmacodynamics

Zolpidem, though not a benzodiazepine, shares some of the pharmacological properties of the benzodiazepines. It interacts with the GABA-BZ receptor complex, preferentially binding the BZ_1 receptor. This receptor is present in the substantia nigra (pars reticulata), ventral thalamic complex, pons, and globus pallidus, among other places. Receptor specific binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses and the relative absence of myorelaxant and anticonvulsant effects in animal studies.

4.3.2 Pharmacokinetics

The pharmacokinetics review is being performed by Dr. Jagan Parepally. The interested reader is referred to his final review for a detailed review on the pharmacokinetics of this product, Zolpidem tartrate sublingual tablet in reference to the reference listed drug Ambien.

5 Sources of Clinical Data

Table 1: Tables of Clinical Studies

Study Number Design	Phase	Objective	Outcome	Study ARM Drug/Control	Population / Age Subjects evaluated	Study Sites Study Dates	Review Section
Pharmacodynamic Study – IND 69200							
0X22-006 Multi-center, randomized, Active-Control, double-blind, *double-dummy*, 2-period CO study of *single doses* of Zolpidem tartrate sublingual tablets Vs. Ambien	2	To evaluate the hypnotic effects on sleep initiation by PSG of a *single dose* of sublingual zolpidem versus oral immediate-release zolpidem (Ambien) in patients with primary chronic insomnia.	Primary Sleep initiation - LPS (to test for Superiority) Sleep maintenance - TST, WASO (at least as good as) Secondary Sleep initiation – SOL, ST1L Other PSG data and subjective assessments of sleep and next day residual effects	Period 1 10mg Zolpidem tartrate sublingual tablet **AND** matching Placebo to Ambien IR 10mg oral capsule **WO period=7-14days** Period 2 10mg oral Ambien IR capsule **AND** matching Placebo of Zolpidem tartrate sublingual tablet	Age 18< 65 Males 31 Females 42 DSM-IV criteria for primary insomnia and presenting symptoms for at least 3 months in duration 72 patients planned 73 randomized 70 per protocol 73 safety analyses 70 PSG analyses	Belgium-322 France-331,332 Russia-701,702,703, 704,705 **3 sites in Belgium pooled recruited patients into one center (322) Dec 2006-July 2007	5.3.2.1
Pharmacodynamic Study – Done Using non-FDA approved comparator to RLD							
0X22-002 Open Label, randomized, single dose, Single Center, 3-period CO study Non-IND	1	To evaluate the hypnotic efficacy and safety of *single dose* of sublingual zolpidem 5 mg and 10 mg compared to oral zolpidem (Stilnoct®) 10 mg *Healthy volunteers*	Primary Sleep initiation-LPS Secondary Other PSG data and subjective assessments of sleep and next day residual effects	5 mg Zolpidem tartrate sublingual tablet OR 10 mg Zolpidem tartrate sublingual tablet OR 10mg Stilnoct®	Age 18- 40 Males 4 Females 17 18 planned 21 randomized 18 per protocol 21 safety analyses 18 PSG analyses	France-1 June 2004-October 2004	5.3.2

Bioequivalence/Bioavailability study – Done Using non-FDA approved comparator to RLD							
0X22-001 Open Label, Single Center, 3-period CO study <u>Non-IND</u>	1	BA & dose proportionality of 5mg and 10mg Zolpidem tartrate sublingual tablets and 10mg Stilnoct® *Healthy volunteers*		5mg Zolpidem tartrate sublingual tablet OR 10mg Zolpidem tartrate sublingual tablet OR 10mg Stilnoct®	Age 18-40 Males 8 Females 10 18 subjects planned/ 18 randomized/ 18 per protocol/ 18 safety analyses	Sweden-1 June 2004	
0X22-004 Open Label, Single Center, 2-period CO study <u>Non-IND</u>	1	BA of 2 different formulations of 10mg Zolpidem tartrate sublingual tablets (OX 22) – *FED condition* *Healthy volunteers*		Formulation – I 10mg OX 22 OR Formulation – II 10mg OX 22	Age 18- 40 Males 8 Females 4 12 subjects planned 12 randomized 12 per protocol 12 safety analyses 12 PK analyses	Sweden-1 June 2005- July 2005	
0X22-005 Open Label, Single Center, 3-period CO study <u>Non-IND</u>	1	To assess PK profile of 10mg Zolpidem tartrate sublingual tablet and 10mg Ambien under fasting and fed conditions *Healthy volunteers*		10mg Zolpidem tartrate sublingual tablet with meal OR 10mg Zolpidem tartrate sublingual tablet fasting OR 10mg Ambien® fasting	Age 18-40 Males 12 Females 6 18 subjects planned 18 randomized 18 per protocol 18 safety analyses 18 PK analyses	Sweden-1 October 2006 -Nov 2006	
0X22-008 Open Label, Single Center,	1	BA of 2 different formulations of 10mg Zolpidem tartrate sublingual tablets (OX 22) – *FASTING*		Formulation – II 10mg OX 22 OR	Age 18-40 Males 7 Females 12 18 subjects planned 19 randomized	Sweden-1	

2-period CO study Non-IND		*condition* *Healthy volunteers*		Final Commercial Product 10mg OX 22	18 per protocol 19 safety analyses	August 2007-Sept 2007	
***Safety** Study – IND 69200*							
0X22-007 Open Label, Single Center, *Multiple-dose* 60-day study	2	Chronic insomnia patients (difficulty initiating or maintaining sleep or non-restorative sleep lasting for at least 1 month prior to the pre-study visit)	Evaluate local tolerance and safety of sublingual Zolpidem tartrate sublingual tablets	10mg Zolpidem tartrate sublingual tablet	Age 18-64 Males 20 Females 40 60 patients planned/ 60 enrolled/ 53 per protocol/ 60 safety analyses	Idaho, USA April 2007-Oct 2007	5.3.3

5.1 Review Strategy

The Sponsor's submission was emphasized in this review. All the trials were included in the analysis of safety.

I, Dr. Suhail Kasim, am responsible for the review and documentation of the clinical trials data including both safety and efficacy analysis.

Dr. Jagan Parepally, of the Office of Clinical Pharmacology and Biopharmaceutics, reviewed the pharmacokinetic and bioequivalence data.

Dr. Melissa Banks is the pharmacology/toxicology reviewer.

5.1.1 Indication – Short Term Insomnia

Zolpidem tartrate sublingual tablet is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

5.2 Discussion of Individual Studies

Below is a figure adapted from the sponsor's submission about the OX22 - sublingual zolpidem tartrate clinical development program and the formulations used in their development. Briefly, three formulations namely Formulation I, Formulation II and the Final Commercial Product (FCP) were developed and used in initial and pivotal clinical studies. Formulation I was compared to non-FDA approved product (Stilnoct®) to demonstrate Bioequivalance (BE) and Pharmacodynamic (PD) effects through studies OX22-001 and OX22-002. Following FDA meetings, Formulation II was developed with bridging BE/PK study to Formulation I through study OX22-004. The BE/PK and PD effects of Formulation II was compared to Ambien® in studies OX22-005 and OX22-006. Although no direct comparison was made between FCP and Ambien®, a BE/PK study OX22-008 was done between Formulation II and FCP to show the same. Finally, a local tolerability study using FCP was conducted in study OX22-007. The sponsor intends to market the Final Commercial Product as zolpidem tartrate sublingual tablets.

Details of the compositions of these formulations will follow in subsequent sections.

Figure 1: OX22 Clinical Development Program

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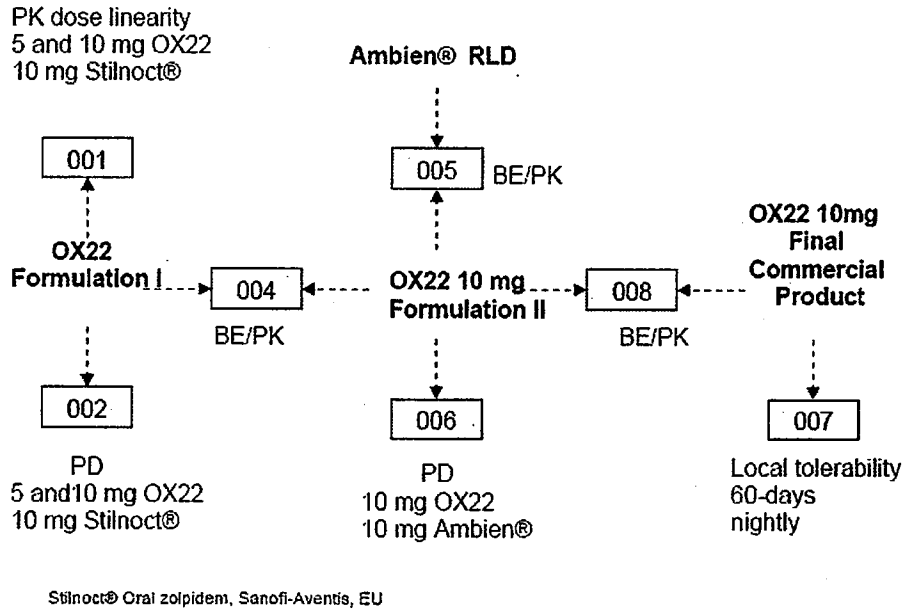
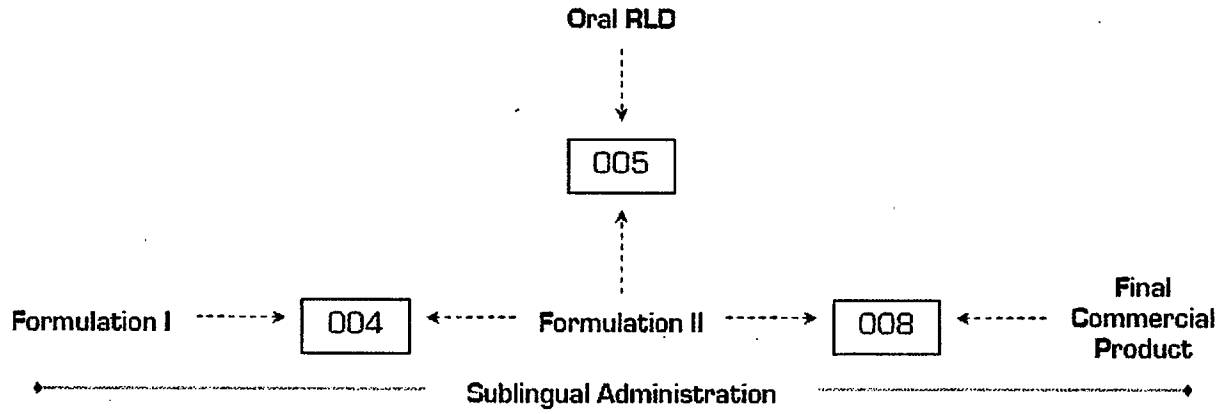
Figure 1: OX22 Clinical Development



Stilnoct® Oral zolpidem, Sanofi-Aventis, EU

Orexo AB believes that studies OX22-004, in conjunction with OX22-005, bridge the early development formulation (Formulation I), the later development formulation (Formulation II), and the RLD, Ambien®. Furthermore, study OX22-008 bridges Formulation II to the Final Commercial Product (FCP) as well as Ambien®. The sponsor intends to market Final Commercial Product (FCP) for short term insomnia. Two studies, OX22-007 (60 day local sublingual tolerability study) and study OX22-008 (BE/PK bridging study between FCP and Formulation II) were conducted with the FCP. No study made direct comparison between FCP and Ambien®.

Figure 2: OX22 Clinical Development Program



The above figure was adapted from the submission.

5.2.1 Summary of Clinical Pharmacology Trials

OX22-001: This study conducted in Sweden was an open label randomized, three-period crossover, single-centre study that compared bioavailability and to evaluate the pharmacokinetic profiles of Formulation I sublingual zolpidem 5 mg and 10 mg, to that of Stilnoct® oral zolpidem 10 mg (not approved for use in USA). Dose proportionality and linearity of zolpidem tartrate sublingual tablets 5 and 10 mg doses (Formulation I, OX22) was established.
Dose: Single doses during each of the crossover periods.
N=18. There were no withdrawals or dropouts. All subjects were included in the primary and secondary pharmacokinetic and efficacy analyses, and in the safety analysis.
Patient population (18-40 years): Healthy male (8) and female (10) volunteers.

OX22-004: This study was conducted in Sweden. A comparative pharmacokinetic evaluation was made between the early development Formulation I (10 mg OX22), and later development Formulation II (10 mg OX22). Both were given as single dose after fasting in 12 healthy subjects 18-40 years of age. Orexo AB belives that this study bridges Formulation I and Formulation II.
Dose: Single doses during each of the crossover periods.
N=12. There were no withdrawals or dropouts. All subjects were included in thepharmacokinetic and efficacy analyses, and in the safety analysis.
Patient population: Healthy male (8) and female (4) volunteers, aged 18-40.

OX22-005: This study conducted in Sweden was an open label randomized, three-period crossover, single-centre study to prove bioequivalence and to evaluate the pharmacokinetic profiles of sublingual zolpidem 10 mg (Formulation II) during fasting and fed states with Ambien 10 mg (Reference listed drug).
Dose: Single doses during each of the crossover periods. One dose of sublingual zolpidem was given 20 minutes after a meal.
N=18. There were no withdrawals or dropouts. All subjects were included in the pharmacokinetic and efficacy analyses, and in the safety analysis.
Patient population: Healthy male (12) and female (6) volunteers, aged 18-40.

I have included pertinent findings and results **from the sponsor's submission from the PK/BE** study comparing Formulation II and Ambien®, which shall be summarized in section 5.3.1.1.

Summary of the pharmacokinetic variables of Formulation II and Ambien® (n=18). Mean values and SD

Table 2: Summary of the pharmacokinetic variables

Pharmacokinetic parameter	OX22 Formulation II with meal	OX22 Formulation II fasting	Ambien® fasting
AUC0-t (min*ng/ml)	18847 (5645)	24295 (10046)	23077 (10992)
AUC0-∞ (min*ng/ml)	20097 (6764)	25740 (11027)	24733 (12741)

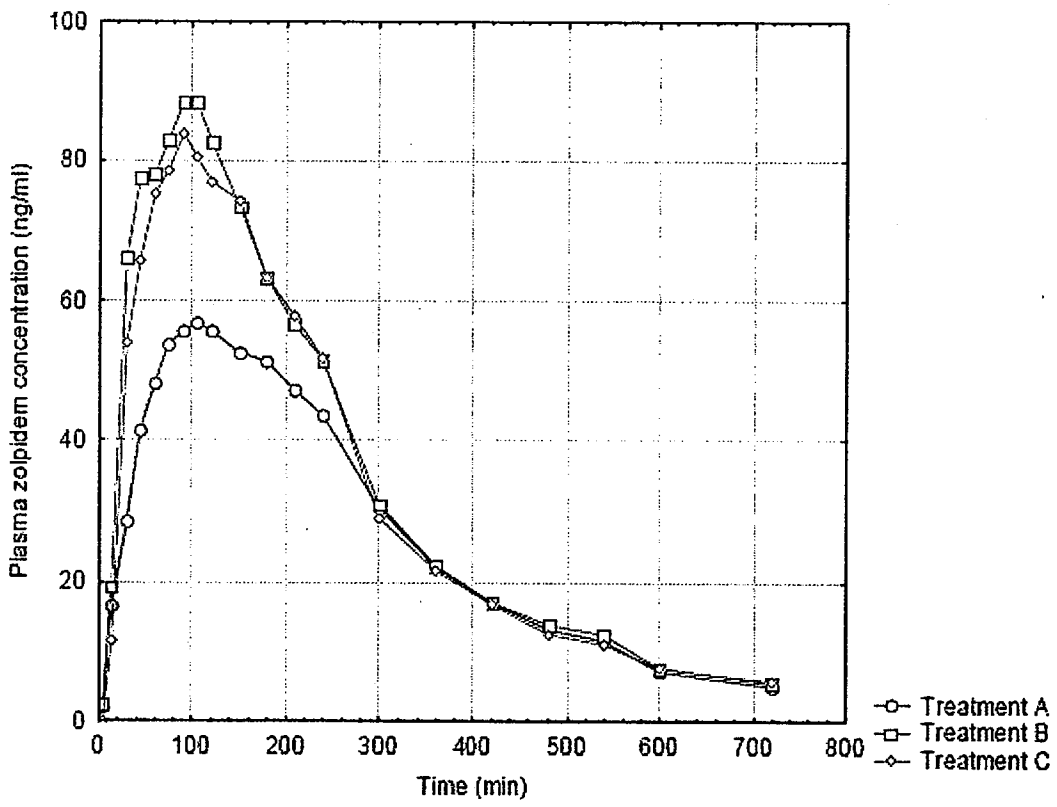
Cfirst (ng/ml)	3.9 (2.5)	8.4 (9.9)	11.8 (18.5)
Cmax (ng/ml)	70.5 (18.8)	106.2 (42.7)	102.3 (41.7)
tmax (min)	105 (30-240)	82 (30-180)	90 (30-180)
t1/2 (hr)	2.39 (0.61)	2.65 (0.58)	2.69 (0.83)

Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals.

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
Formulation II Fasting/Ambien Fasting	$AUC_{0-\infty}$	107.6	98.6	117.5
	C_{max}	106.0	91.7	120.1

Mean plasma concentrations following administration of Formulation II sublingual zolpidem 10 mg tablet and Ambien® tablet under fasting and fed conditions.
A = OX22 Formulation II with meal, B = OX22 Formulation II fasting, and C = Ambien® fasting

Figure 3: Mean plasma concentrations



OX22-008: This study conducted in Sweden was an open label randomized, two-period crossover, single-centre study to prove bioequivalence and to evaluate the pharmacokinetic profiles between sublingual zolpidem 10 mg (formulation II) and the final commercial product sublingual zolpidem 10 mg (FCP-Zolpidem tartrate sublingual tablets).
Dose: Single doses during each of the crossover periods.
N=19. There were no withdrawals or dropouts. All subjects were included in the pharmacokinetic and efficacy analyses, and in the safety analysis.
Patient population: Healthy male (7) and female (12) volunteers, aged 18-40.

I have included pertinent findings and results **from the sponsor's submission from the PK/BE** study comparing Formulation II and Final Commercial Product (FCP), which shall be summarized in section 5.3.1.1.

Table 3: Summary of the pharmacokinetic variables

Summary of the pharmacokinetic variables of Formulation II and Final Commercial Product (FCP) (n=18). Mean values and SD.

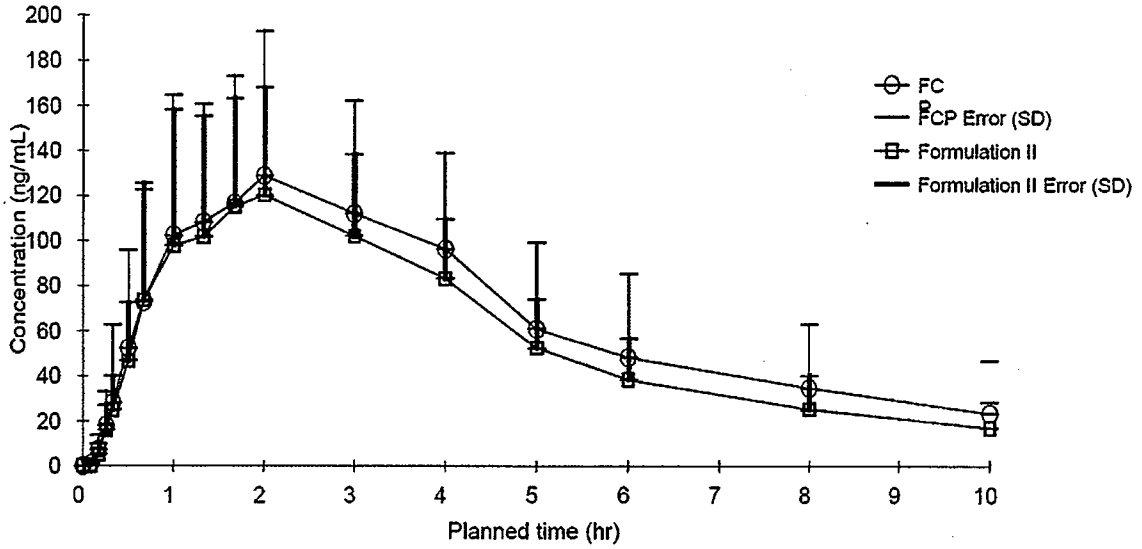
Parameter	Formulation II (N = 18)	Final Commercial Product (FCP) N = 18
AUC0-t (ng*h/mL)	579.8 (222.5)	663.3 (310.1)
AUC0-∞ (ng*h/mL)	663.3 (287.3)	786.1 (443.5)
Cfirst (ng/mL)	3.16 (3.08)	3.45 (4.29)
Cmax (ng/mL)	133.40 (47.1)	148.39 (62.5)
Tmax (h)	2.00 (1.00 - 4.00)	2.00 (0.33 - 3.00)
T 1/2 (h)	2.89 (2.02 - 4.67)	2.68 (1.76 - 5.56)

Pharmacokinetic Parameter Ratios of Point Estimates and 90% Confidence Intervals.

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
FCP/ Formulation II	$AUC_{0-\infty}$	112.0	81.4	98.63
	C_{max}	108.0	84.5	101.4

Figure 4: Mean plasma concentrations

Mean plasma concentrations following administration of sublingual zolpidem 10 mg tablet Formulation II and Final Commercial Product (FCP).



Orexo AB believes that studies OX22-004, in conjunction with OX22-005, bridge the early development formulation (Formulation I), the later development formulation (Formulation II), and the RLD, Ambien®. Furthermore, study OX22-008 bridges Formulation II to the FCP. The bridge between the pharmacokinetic profile including the sleep and laboratory polysomnography or pharmacodynamics (PSG or PD) effects of OX22 10 mg Formulation II and Ambien was made by comparing results of the OX22-005 and OX22-006 studies.

I copied the following table containing composition of different formulations used in the clinical studies.

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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		
		-	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	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.

5.2.1.1 Reviewer conclusions based on pharmacokinetic parameters

I used the pharmacokinetic results provided by the sponsor, in order to make these conclusions. Study 005 compared formulation II to Ambien, and study 008 compared formulation II to the final formulation (FCP), however study comparisons were not made between FCP and Ambien. The pharmacokinetic parameter ratios of point estimates and 90% Confidence Intervals for Formulation II Fasting/Ambien Fasting were within 80% to 125% of reference product for AUC and Cmax. Similar results for AUC and Cmax were obtained for FCP/Formulation II. These results establish bioequivalence of the sublingual product with the RLD Ambien.

The PK studies have established that the final formulation is bioequivalent to the currently marketed dose of Ambein. The drug safety profile is similar to the reference listed drug, Ambien. Safety data is discussed in section 7.

5.2.2 Summary of Efficacy Trials

Pharmacodynamic Polysomnography (PSG) sleep parameters Description
Two kinds of sleep parameters are derived from the visual analysis of sleep:

- Sleep *continuity* parameters comprise both sleep initiation and sleep maintenance variables.
    - Sleep *initiation* indicates how easy the patient fall asleep and the time needed to reach stable persistent sleep.
    - Sleep *maintenance* include general parameters that roughly indicated how sleep was maintained after sleep onset (total sleep time, sleep efficiency, and wake after sleep onset) as well as more subtle indicators of maintenance disturbances such as sleep fragmentation indices and intrasleep arousal, wake and awakenings.
- Sleep *architecture* parameters comprise stages 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.

Latency to Persistent Sleep (LPS)
LPS is a sleep initiation parameter; it reflects the ease with which the patient fall asleep and the time needed to reach stable persistent sleep. It is calculated as the latency (in min) from lights-off (i.e. when the sleep recording started) to the appearance of the first epoch of either stage 2, 3, 4 or 5 that is followed by 20 consecutive epochs of non wake (i.e. of either stage 1, 2, 3, 4, 5 or 6).

Sleep onset latency (SOL)
Sleep onset is the first appearance of an epoch scored as stage 2. Accordingly, SOL is also a sleep initiation parameter; it merely reflects the ease with which the patient reached the first epoch of sleep, whether or not the sleep was stable and persistent. It is calculated as the latency (in min) from lights-off (i.e. when the sleep recording started) to the appearance of the first epoch of stage 2 (regardless of if this epoch was followed by wake or not).

Latency to stage 1 (ST1L)
ST1L is a third sleep initiation parameter. Since stage 1 is an intermediary stage between wake (stage 0) and sleep onset (stage 2); this parameter merely reflects the ease with which the patient reaches a state of pre-sleep drowsiness. It is calculated as the latency (in min) from lights-off (i.e. when the sleep recording started) to the appearance of the first epoch of stage 1 (regardless of if this epoch is followed by wake or not).

Total sleep time (TST)
TST is a sleep maintenance parameter that roughly indicates how sleep is maintained after sleep onset. It is calculated as the sum of the time (in min) spent in epochs scored either in stage 1, 2, 3, 4 or 5 from sleep onset to lights on (i.e., when the recording ended).

Wake after sleep onset (WASO)
WASO is another sleep maintenance parameter that also indicates how sleep is maintained after sleep onset. It is calculated as the sum of the time (in min) spent in epochs scored as stage 0 (wake) from sleep onset to lights on (i.e., when the recording ended).

OX22-002: This phase I study was conducted in France.

This is a summary table for Study OX22-002

Design	Single-center, randomized, OPEN LABEL, 3-period cross-over study; HEALTHY subjects		
Duration	3-period cross-over study		
Key Inclusion Criteria	- Male or Female 18-40 years old - Healthy subjects.		
Primary Outcome Measures	Latency to Persistent Sleep (LPS): Time from light off to the first 20 epochs of either stages 2,3,4 or REM		
Population for Primary efficacy Analysis	All patients will be included in the efficacy analyses. Sleep Initiation: -Paired t-test, one-sided for LPS (to test for superiority; 5mg, 10mg Sublingual Zolpidem tartrate > 10mg oral Stilnoct).		
Secondary Outcome Measure	Sleep Initiation: -Two-sided t-test for Sleep Onset latency (SOL), Latency to Stage 1 (ST1l.)		
Dose Arms	Sublingual Zolpidem tartrate (5mg OX 22)	Sublingual Zolpidem tartrate (10mg OX 22)	10 mg Stilnoct
Number Randomized	21	21	21
Number Completing	18	18	18

Design/Objective: This open label randomized, three-period crossover, single-centre polysomnograph study evaluated the hypnotic efficacy and safety of sublingual zolpidem 5 mg and 10 mg (Formulation I) with oral zolpidem 10mg, Stilnoct® (product not approved for use in USA).
Dose: Single doses during each of the crossover periods.

N=21 randomized; 18 completed subjects (per protocol) whose polysomnogram results were analyzed.
Patient population: Healthy male (12) and female (6) volunteers, aged 18-40.

Using a post-nap model (2-hour nap) in healthy volunteers who were fasting 3 hours prior to dose, efficacy variables from polysomnogram results were analyzed.

The primary efficacy variable for *sleep initiation* was latency to persistent sleep (LPS), measured as change from baseline.

The secondary variables:

Sleep initiaition (variables measuring ease to get to sleep):
- Latency to stage 1 (ST1L)
- Sleep onset latency (SOL)

Sleep maintenance:
- Sleep period time (SPT), interval separating sleep onset from the last sleep epoch
- Number of awakenings after sleep onset (WASO)
- Total time awake (TTA), total duration of wake epochs during time in bed (TIB) that correspond to the recording period
- Total sleep time (TST), total duration of sleep epochs after sleep onset
- Microarousal index (MAI), number of microarousals per TST hours
- Sleep efficiency index (SEI: ratio of TST to TIB)

Subjective assessment of sleep and evaluation for next day 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

- Key study eligibility criteria: Individuals with BMI <19 or >30 were excluded from the study.
- Non-smoker and no use of alcohol 24 hours prior to each treatment session, daily alcohol use restricted to less than 40g per day, and coffee/coke restricted to less than 5 cups per day.
- Should not be a drug abuser, or take any CNS influencing medication within 6 weeks prior to screening visit.
- Should not have history of head injury, seizures, cerebrovascular disease, or other neurological disease. Absence of psychiatric illness including depression and anxiety or primary sleep disorderincluding any sleep disorders having a score more than 5 on the Pittsburgh Sleep Quality Index. Should not be doing shift work.
- Should not have gastrointestinal, hepatic or renal disease or other condition.

The concomitant medications were administered at the discretion of the investigator.

Phases of study:

Screening phase:	1 day within 7 and 28 days prior to the first dosing, followed by an ambulatory 5-day period with actimetry from D-7 to D-2.
Assessment periods:	3 assessment periods in the center, one lasting 3.5 days and the others 2.5 days each.
Wash-out period:	At least 7 days between each dosing occasion. Regular sleep/wake schedule assessed during 5 days preceding the inclusion in period 2 and 3.
End-of-study visit:	5 to 7 days after the last dosing

Duration of the study: The screening study results from polysomnography testing and actigraphy would inform eligibility. There were three assessment periods. On D-1 (baseline) and on Day 1 (dosing day D1), the subjects were to take a nap from 16:00 to 18:00. *Dosing would begin at 22:30 on D1 of each treatment period (three periods – 1,2,3).* For the first assessment period, the subject would be observed for 3.5 days. There would be at least 7 days wash out period between each dose tested. During the second and third assessment period, the subject would be observed for 2.5 days each. 5-7 days after the last dose the study would conclude with a final visit.

This summary study flow chart with investigational schedule was copied from the Sponsor's submission

Table 4: OX22-002 Investigational Schedule

Appears This Way
On Original

	Screening		Assessment period 1				Min.7-days Wash-out period Between dosings	End of study
				Periods 2 and 3				
	D-28	D-7 to D-2 (ambulatory)	D-2	D-1	D1	D2	5 days preceding inclusion in period 2 and 3	5-7 days after last dosing
Clinical assessments								
Physical exam	X		X			X**		X
Medical history	X							
BP/HR	X		X	Xd	X*	X**		X
ECG	X		X	Xd	X*	X**		X
Psychological exam	X							
Standard EEG	X							
AE recording		X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Actimetry		X	X	X	X	X	X	
Leeds Sleep questionnaire					Xb	X		
VAS Bond and Lader					Xb	X		
Leeds psychomotor tests	Xc				Xb	X		
DSST	Xc				Xb	X		
Biological assessments								
Blood chemistry/ haematology	X		X			X**		X
Serology	X							
Urine biochemistry	X		X			X**		X
Urine drug screen	X		X	Xd				
Pregnancy test	X		X	Xd				X
Drug administration					X			
Pharmacodynamic assessments								
Sleep questionnaire (PSQI)	X							
Horne and Ostberg questionnaire	X							
Polysomnography			Xa	Xb	X			
Nap				X	X			

*once before administration **before discharge, period 3 only
a: habituation night b: baseline c: training d: period 2 and 3 only

Handling of subject withdrawal: The reasons for withdrawals required documentation in the CRFs. If possible a "final study visit" was to be performed for these subjects who received the IMP but did not complete the study as "per protocol."

Subjects were considered evaluable for the study (per protocol) if at least one nap out of 3 on D-1 (baseline) displayed a sleep duration of at least 30 minutes, and if all of the 3 treatment periods were evaluable.

Statistical Analysis: By using the number needed to treat criteria and from gaboxadol study results, the Sponsor used an overall power of 30% (α=5%) to detect a 10 minute difference in mean latency to persistent sleep (LPS) between the sublingual and oral formulations. Therefore 18 subjects were determined for analysis.

Two populations were considered:

- "Safety Population": The total treated population consisted of all subjects who were randomized and took at least one dose of the investigational product, including any replacement subjects if applicable were to be included in the safety analysis.
- "Per protocol population": Not all the patients who were randomized would be included in the ITT analysis. "Only the subjects who were evaluable for the study will be included in the pharmacodynamic analysis. The 'Safety Population' and the 'Per protocol population' would be defined just before the statistical analysis."

The primary efficacy variable LPS (latency to persistent sleep), was compared between the treatments in a three-period crossover analysis using SAS with patient, period, and treatment as class variables. Paired differences between the sublingual (5, 10 mg) and the oral treatment was estimated and tested within the statistical model (paired t-test). No interim analysis was performed.

Primary Variable:
Latency to Persistent Sleep (Sleep initiation): Latency from "lights off" to the first 20 continuous epochs of either ST2, ST3, ST4 or REM.

STUDY RESULTS

Trial characteristics: The study was conducted at one center in Rouffach, France. A total of 21 patients were enrolled and randomized; 18 completed the study.

The patient Demographics and baseline characteristics are listed below which was copied from the Sponsors submission.

Randomised (n)	**21**
Sex	
• Female (n)	17
• Male (n)	4
Age	**Mean age (range)**
• Female	25.7 (±4.3)
• Male	30.9 (±7.9)
• All	26.7 (±5.3)
Body Mass Index	22.7 (±3.0)
Height (cm)	169.6 (±8.9)
Weight (kg)	65.6 (±11.5)
Life style	
• Smokers (n)	0
• Consumers of xanthine-containing beverages (coffee or cola) (n)	12
• Positive drug screen (n)	0
• Positive serology (n)	0

Primary Efficacy parameter results:
The Sponsor's analysis demonstrated that there was a statistically significant difference between the sublingual and oral 10mg doses of Zolpidem with regard to the three sleep initiation variables including the primary efficacy variable, latency to persistent sleep (LPS). Results are shown below. The duration for sleep initiation as demonstrated by LPS duration was shortened by 6.11 minutes.

Study OX22-002, Sleep Initiation Parameter Results

Variables	OX22 5 mg (min)	OX22 10 mg (min)	Stilnoct (min)	Difference OX22 5mg-Stilnoct	Difference OX22 10mg-OX22 5mg	**Difference OX22 10mg-Stilnoct**
LPS	19.53 (11.49)	12.79[1] (9.91)	18.36 (11.29)	1.167 (NS)	-7.279 (p=0.013)	**-6.112 (p=0.034)**
ST1-L	16.56 (9.10)	10.50 (7.03)	16.67 (10.17)	-0.111 (NS)	-6.056 (p=0.012)	**-6.167 (p=0.011)**
SOL	20.86 (11.23)	14.17 (7.65)	19.97 (11.16)	0.889 (NS)	-6.694 (p=0.010)	**-5.806 (p=0.024)**

The results are expressed as raw mean minutes (SD).
For differences, estimates (p-values) are from an ANOVA model.
NS= not statistically significant
[1]: calculated on the data from 17 subjects, due to an outlying value.

(taken from page 30/50 of the study report)

There were no statistically significant differences among any of the variables demonstrating sleep architecture or sleep maintenance.

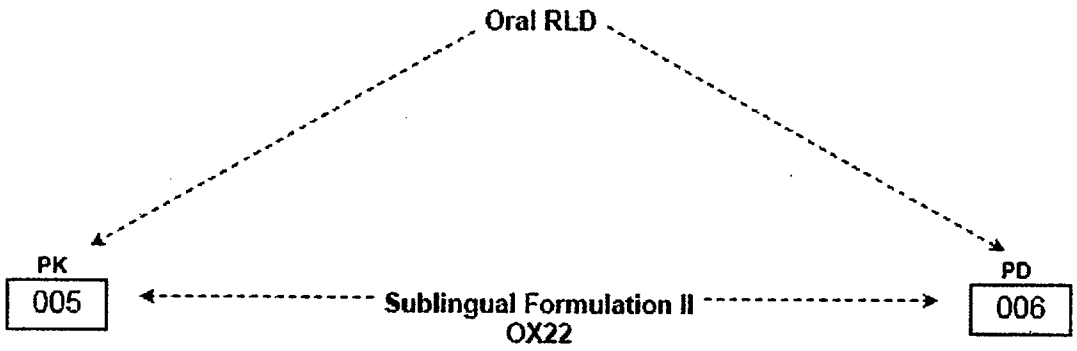
OX22-002 Reviewer Efficacy conclusions:
This open label study demonstrated that in healthy adults the sublingual formulation of 10mg Zolpidem was able to shorten the duration to fall asleep by 6.11 minutes compared to an oral formulation of 10mg Zolpidem that was available for use in Europe, and this result was supported by the other secondary efficacy variables for sleep initiation. However, since this study is not comparable to the reference listed drug Ambien®, the results cannot be included in the label. In addition, it was an uncontrolled study conducted in healthy subjects.

5.2.2.1 OX22-006 Clinical Effects: Pharmacodynamic Trial

This Phase 2 multicenter, double-blind, randomized, two period crossover study was conducted in 73 primary chronic insomnia patients (18-65 years of age) meeting the DSM-IV criteria and presenting appropriate symptoms to evaluate the hypnotic effect of single dose zolpidem tartrate sublingual tablet Formulation II (10 mg, OX22) compared to single dose 10 mg Ambien®.

Rationale for conduct of study as discussed prior to NDA submission:
To demonstrate a Pharmacokinetic/Pharmacodynamic bridge between OX22 Formulation II and Ambien® in support of the 505 (b)2 NDA.

Figure 5: PK/PD studies comparing OX22 Formulation II with Ambien®



NOTES:

- PK = pharmacokinetics; PD = pharmacodynamics (polysomnography sleep effects); RLD = Reference Listed Drug
- 005 = OX22-005, a single center, open, randomized, three period, crossover study in 18 (per protocol) healthy subjects, 18-40 years of age comparing PK following sublingual administration of Formulation II (10 mg OX22) and oral administration of 10 mg Ambien®, the RLD. Determination of the pharmacokinetic effects of a meal was also made for OX22.
- 006 = OX22-006, a multicenter, double-blind, randomized, two period crossover study in 70 (per protocol) insomnia patients, 18-65 years of age, evaluated the hypnotic effect of OX22 Formulation II (10 mg of OX22) compared to 10mg Ambien®, the RLD.

b(4)

The study is summarized in the table below.

Design	Multi-center, randomized, double-blind, double-dummy, 2-period cross-over study; SINGLE DOSE
Duration	2-period cross-over study
Key Inclusion Criteria	- Male or Female 18-65 years old - Chronic primary insomnia (difficulty initiating or maintaining sleep or of nonrestorative sleep that lasts for at least 3 months) - On two consecutive screening nights the subject has a TST < 6.5 h, a duration of WASO > 30 min and a LPS of ≥20 minutes with a mean LPS greater than 30 min. No LPS <20 min and (LPS1+LPS2)/2 >30 min.
Primary Outcome Measures	Latency to Persistent Sleep (LPS) - to test for superiority

Population for Primary efficacy Analysis	All patients will be included in the efficacy analyses. Sleep Initiation: -Paired t-test, one-sided for LPS (to test for superiority; 10mg Sublingual Zolpidem tartrate > 10mg oral Ambien IR).	
Secondary Outcome Measure	Sleep Initiation: -Two-sided t-test for SOL, ST1l. Sleep Continuity/Maintenance: - Two-sided t-test (tested for non-inferiority): for TST and Number and duration of WASO.	
Dose Arms	one **Zolpidem tartrate sublingual tablet** 10 mg and one capsule of the matching **placebo** to oral 10 mg Ambien IR	one capsule of 10 mg **Ambien** IR and one matching **placebo** sublingual tablet to Zolpidem tartrate 10 mg.
Number Randomized	73	73
Number Completing	72	72
Number analyzed for Efficacy	70	70

This study was conducted at 8 centers as per the study protocol. The patients were recruited across ten centers; two in France, five in Russia, and three in Belgium. For balanced design and statistical analysis the centers were grouped into 4:

Centers	Number of subjects
Belgian and French (322, 331, 332)	1+13+5=19
Russian: Yekaterinburg (701, 702)	17+2=19
Russian: St Petersburg and Vladimir centers (704, 705)	7+7=14
Moscow study centre (703)	21

The final version of the protocol dated 08/23/2006 is summarized below. Additional information clarifying methods for PSG recordings and transfer of recorded PSG data to the CRO was sent by the Sponsor on 8/15/2008. It does not appear that further amendments have been made to the protocol since the study blind was broken.

Objective

To demonstrate that Zolpidem tartrate sublingual tablet is superior to oral Ambien, assessed by polysomnograph parameters, in patients with primary chronic insomnia.

The primary sleep initiation endpoint variable is LPS (Latency to Persistent Sleep). Other endpoints for sleep initiation: SOL (Sleep Onset latency), and ST1L (Latency to Stage 1); and for sleep maintenance include: TST (Total Sleep Time), WASO (Number and duration of awakenings after sleep onset); and patient reported subjective assessment of sleep and next-day residual effects.

Design, Dose, Sample Size and Duration

Phase II, Multi-center, randomized, double-blind, double-dummy, 2-period cross-over study that compared the pharmacodynamic effects of 10mg Zolpidem tartrate sublingual tablet to 10mg oral Ambien IR in 73 subjects when subjected to overnight PSG studies. A 7 day wash-out period was included in between treatment periods.

The double-dummy was chosen to ensure study drug blinding since 10mg Zolpidem tartrate sublingual tablet and 10mg oral Ambien IR are administered through different routes and cannot be made identical.

Key Inclusion Criteria

- Female or male aged 18 to 65 years old.
- Non-pregnant and non-lactating females. Females of childbearing potential must use appropriate birth control (barrier methods, hormonal contraceptives, and/or intrauterine devices) for the entire duration of the study.
- The subject has a body mass index (BMI) between 18 and 30, inclusive.
- Primary chronic insomnia according to DSM-IV criteria:
    - Difficulty initiating or maintaining sleep or of nonrestorative sleep for at least 3 months.
    - The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
    - The disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder or Parasomnia.
    - Sleep disturbance does not occur exclusively during the course of mental disorder (eg, Major Depressive Disorder, Generalised Anxiety Disorder, delirium).
    - The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.
- On two consecutive screening nights the subject has a TST < 6.5 h, a duration of WASO > 30 min and a LPS of ≥20 minutes with a mean LPS greater than 30 min. No LPS <20 min and LPS1+LPS2)/2 >30 min.

Key Exclusion Criteria

- Known hypersensitivity to zolpidem or related compounds.
- Participation in any other investigational study and/or taken any investigational drug within 30 days (or five half-lives of the drug, whichever is longer) prior to screening.
- Sleep schedule changes required by employment (eg, shift worker) within three months prior to screening, or has flown across greater than three time zones within seven days prior to screening.
- History of seizures; sleep apnea, chronic obstructive pulmonary disease, restless leg syndrome, periodic leg movement syndrome, schizophrenia, bipolar disorder, mental retardation, cognitive disorder or fibromyalgia.

- History of psychiatric disorder (including anxiety and depression) within the past 6 months.
- History of alcohol abuse or drug abuse within the past 12 months.
- Significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, haematological, or metabolic disease, unless currently controlled and stable with protocol-allowed medication 30 days prior to screening.
- Used drugs or supplements known to affect sleep/wake function within 1 week (or 5 half lives of the drug, whichever is longer) prior to screening.
- Any central nervous system medication use within 1 week (or 5 half lives of the drug, whichever is longer) prior to screening.
- Clinically important abnormal finding as determined by a medical history, physical examination, ECG, or clinical laboratory tests, as determined by the investigator.
- Positive urine drug screen including alcohol at screening or at check-in.
- Positive pregnancy test (serum hCG) at screening or at check-in.
- Apnoea hypopnoea index (per hour of sleep) >10 as seen on PSG, on the first night of the PSG screening.
- Periodic leg movement (PLM) with arousal index (per hour of sleep) >10 as seen on PSG, on the first night of PSG screening.
- Alcohol consumption > 40 g alcohol/day.
- Use of more than 10 cigarettes or equivalent/day.
- Positive test result on hepatitis B surface antigen, hepatitis C antibody.
- Positive test for HIV-1, HIV-2.
- Excessive daily consumption of xanthine containing drinks (i.e > 500 mg/day of caffeine)

Concomitant Medications

No concomitant medications were permitted during the study period unless it had been excused and allowed to be used with consent of the Investigator. Females were allowed oral contraceptive use.

Study Schedule

The study schedule is summarized in the following table and I have copied it from the submission.

	Screening				Assessment Periods 1 and 2			End of Study
	S1	S2	S3	S4	Day –1	Day 1	Day 2	
Screening procedures								
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical/sleep history	X							
Height / Weight	X							
Blood serology	X							
Alcohol breath test	X	X			X			
Urine drug screen	X	X			X			
IMP administration						X		
Safety assessments								
Physical examination	X				X		X	X
Vital signs	X				X	X	X	X
ECG	X				X		X	X
Laboratory tests	X				X			X
Adverse events		←	—	—	—	—	→	
Prior and concomitant therapies	←	—	—	—	—	→		
Pharmacodynamics								
Sleep EEG		←	—	→ [c]		← → [d]		
Leeds Sleep questionnaire							X	
Leeds psychomotor tests			X[a]			X[c]	X	
DSST			X[b]			X[c]	X	
VAS						X[c]	X	

[a]: Five training sessions [b]: One training session [c]: Baseline [d]: Habituation night

Detailed Study Schedule Per Period

Day	Day -1				Day 1			Day 2			
Clock time	8:00	23:00	7:00	7:30				23:00	7:00	7:30	10:00
IMP administration								X			
Physical examination	X										X
Vital signs	X							X			X
ECG	X										X
Alcohol breath test	X										
Urine drug screen	X										
Laboratory tests	X										X
Sleep EEG		←	—	→ [a]				← → [b]			
Leeds Sleep questionnaire										X	
Leeds psychomotor tests, DSST, VAS				X[c]						X	
Adverse events	←	—	—	—	—	—	—	—	—	—	→
Concomitant therapies	←	—	—	—	—	—	—	—	—	—	→

[a]: Habituation night
[b]: Recorded night
[c]: Baseline

STUDY RESULTS

Demographic characteristics are summarized in the following tables below.

		Pooled center 1		*Pooled center 2*		*Pooled center 3*		*Pooled center 4*		*All patients*	
		Female n=10	*Male n=9*	*Female n=13*	*Male n=6*	*Female n=9*	*Male n=5*	*Female n=10*	*Male n=11*	*Female n=42*	*Male n=31*
Age (years)	Mean ± SD	42.5 ± 11.6	39.2 ± 6.7	51.6 ± 8.2	31.7 ± 9.1	40.4 ± 5.7	27.4 ± 5.7	44.9 ± 8.4	38.9 ± 14.3	45.5 ± 9.5	35.7 ± 11.0
	Min - Max	24 - 59	28 - 51	40 - 64	19 - 42	29 - 49	22 - 35	28 - 59	23 - 58	24 - 64	19 - 58
BMI (kg/m^2)	Mean ± SD	22.16 ± 3.10	23.02 ± 1.38	24.86 ± 2.59	25.47 ± 2.36	24.12 ± 1.58	24.80 ± 2.78	26.19 ± 4.36	24.45 ± 3.15	24.38 ± 3.29	24.29 ± 2.57
	Min - Max	18.0 - 26.9	20.4 - 25.1	20.4 - 20.1	22.9 - 28.6	21.5 - 26.0	22.6 - 29.4	19.1 - 29.9	19.8 - 28.8	18.0 - 30.1	19.8 - 29.4

Randomised (n)	73
Sex	
• Female (n)	42
• Male (n)	31
Age	**Mean age (range)**
• Female	45.5±9.5
• Male	35.7±11.0
Body Mass Index	
• Female	45.5±9.5
• Male	35.7±11.0
Life style	
• Smokers (n)	18 (24.7%)
• Consumers of xanthine-containing beverages (coffee or cola) (n)	53 (72.6%)
• Positive drug screen (n)	0
• Positive serology (n)	0
• Alcohol use (n)	18 (24.7%)
• Positive alcohol breath test	0
• Positive pregnancy test (n)	1
o Day 1 in Period 1	

Patient Disposition

158 patients were screened and 73 males and females met study criteria. Among the 85 excluded subjects, 46 did not fulfill PSG criteria during at least one of the two screening nights and 39 patients were excluded for other reasons.

	Dose Arms	
	one **Zolpidem tartrate sublingual tablets** 10 mg and one capsule of the matching **placebo** to oral 10 mg Ambien IR	one capsule of 10 mg **Ambien** IR and one matching **placebo** to Zolpidem tartrate sublingual tablet 10 mg.
Number subjects Randomized	73	73

Number Completed the study	72	72
Number analyzed for Efficacy	70	70
Reason for discontinuation		
Adverse event - pregnancy	1	
Protocol Violation (did not meet PSG criteria)	2	

Major protocol deviations: One patient was withdrawn from the analysis due to pregnancy and miscarriage (No. 701-003) while on the Ambien arm of the study. Two others (No. 322-005 and 703-002) were noted to have major protocol deviations since they did not meet PSG criteria; recordings were not initiated immediately following administering the investigational product.
Minor protocol deviations: I reviewed the submission for protocol deviations and did not identify significant concerns.

Drug Compliance
The double dummy drugs were administered to the **patients' under the control** of the investigator. A check of mouth and hands was performed, and the exact date and time of IMP administration was recorded in source records.

Efficacy Overview

Variables*	Baseline	Zolpidem tartrate 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)

OX22-006 Reviewer conclusions:
The duration to fall asleep was decreased by about 10 minutes in patients who took the *sublingual* formulation of 10mg Zolpidem, compared to the *oral* formulation of 10mg Zolpidem (Ambien), and this result was supported by the other secondary efficacy variables for sleep initiation. The C_{max} was 127 ng/mL and T_{max} 101 minutes with sublingual Zolpidem in 36 adult healthy subjects (compiled data) compared to C_{max} = 121 ng/mL and T_{max} 96 minutes as described in the Ambien label when it was studied in 45 healthy volunteers. There was no head-to-head comparative study between FCP and RLD instead Formulation II was compared to Ambein as in OX22-006.

The result is statistically convincing and on average a patient on sublingual Zolpidem may fall asleep 10 minute sooner even though it takes 5 more minutes to reach T_{max}. In clinical practice patients may benefit from falling asleep slightly earlier and the rest of their sleep may remain unchanged between the oral and sublingual formulation without experiencing next day residual effects.

However the results cannot be included in the label for the following reasons: since patients in this study were not exposed to the study drug and compared to active control for a period of time of at least 6-8 weeks, and the results are not replicated with another clinical study that can demonstrate similar pharmacodynamic effect. These issues were discussed with the sponsor during the regulatory meeings. Please see regulatory history for details.

5.2.3 OX22-007 Summary of Local/Sublingual tolerability Trial

OX22-007: This single center open label clinical trial evaluated the local tolerability and safety of zolpidem tartrate sublingual tablet 10 mg (FCP, OX22) daily, for 60 days given to 53 patients with chronic insomnia.
Dose: 10 mg Zolpidem tartrate sublingual tablets self-administered daily at bedtime daily for 60 days.
Patient population: Adults (18-64 years) diagnosed with chronic insomnia who had difficulty initiating or maintaining sleep or non-restorative sleep lasting for at least 1 month prior to the pre-study visit.
Methods: "The patient was instructed that the sublingual tablet was to be placed directly under the tongue into the deepest part of the oral cavity. It was important that the patient did not move or touch the tablet once it had been administered. The patient was instructed not to swallow the tablet, allowing it to dissolve under the tongue without chewing or sucking. The patient was to keep their mouth closed and not move their tongue for at least 15 minutes. It was not allowable to drink water or other liquids or to eat when taking the tablet."

A visual inspection of the sublingual mucosa was made 5 times during the study by the investigator. At the final visit, the patient filled out a simple questionnaire regarding the treatment of IMP. The patient was also contacted by phone between visits for a compliance check and a check of adverse events (AEs) 14 days after the final visit.

N=60 randomized; 53 completed subjects (per protocol). 7 patients discontinued early.

STUDY ENDPOINTS
Primary Endpoint: degree of erythema of the sublingual mucosa after 60 days of Zolpidem tartrate sublingual tablets (FCP) administration.

The sublingual mucosa was to be visually inspected and findings documented in the CRF during visits 2, 3, 4, 5, and 6.

The following scale was to be used:

Degree of erythema (local reaction)	*Score*
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined mild erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

Secondary Endpoint: To evaluate the patients subjective assessment of treatment with Zolpidem tartrate sublingual tablets using patient questionnaire at the end of the study.

Key study eligibility criteria:

- Patients were excluded if they had diseases affecting the oral cavity that may affect the sublingual mucosa; chewing of tobacco, using snuff or other potential irritant within previous 6 months, use of dental whitening treatments within 1 week of visit 2, and use of orthodontic appliances.
- Patients with psychiatric disorder, including anxiety and depression within past 6 months.
- Any patients who have contraindication to use of Zolpidem.

Pre-study and concomitant medications:
The use of concomitant medications that could have interacted with zolpidem such as anti-psychotics (neuroleptica), soporifics, anxiolytics/sedatives, antidepressants, narcotic analgesics, antiepileptics, anesthetics and antihistamines with sedative effect, and rifampicin were not allowed during the study. Any insomnia medications were not allowed during the study. Use of other sublingual medications was prohibited. Washout of concomitant medications was at the discretion of the investigator.

Treatment compliance: The patients were instructed to take the medication at bedtime. At visit 2 (baseline visit) they were given diaries to record when they took medication. The diary was brought to each follow up visit and the information was transcribed into the CRF. A pill count was made at visits 3, 4, 5 and 6.

The following study design was adapted from the Sponsors submission

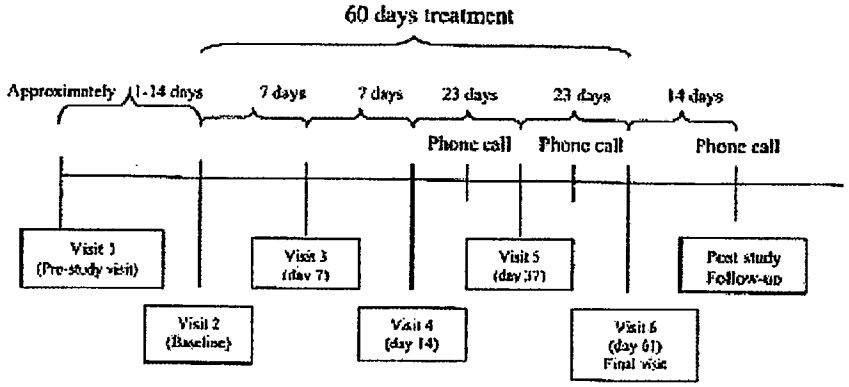


Figure 2

Plan of investigational events

Visit	1 (Pre-study)	2	3	4	5	6 (Final visit)	Follow-up
Informed consent	x						
Demographic data	x						
Inclusion/Exclusion criteria	x	x					
Medical History	x						
Concomitant med.	x	x	x	x	x	x	
Physical exam	x					x	
Weight, Height	x						
Vital signs	x					x	
ECG	x					x	
Laboratory tests[1)]	x					x	
Pregnancy test[2)]	x			x		x	
Urine drug screen	x						
Alcohol breath test	x						
IMP		x	x	x	x		
Visual inspection	x	x	x	x	x	x	
Questionnaire						x	
Adverse Event[3)]		x	x	x	x	x	
Compliance check[4)]			x	x	x	x	
Phone call					x	x	x

[1)] Hematology, clinical chemistry and urinalysis
[2)] For women of childbearing potential only (serum test at visit 1 and urine test at visit 4 and 6)
[3)] Pre-existing conditions will be checked at visit 2
[4)] Pill count and patient diary

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Staistical Analysis Plan: The SAP was decided after study was concluded. Most statistical tests would be conducted at the 5% alpha level. No procedures were outlined for accounting for missing data, unused or spurious data and the Sponsor stated that this was not applicable. Only descriptive and summary statistics would be presented. No interim analysis was planned.

STUDY RESULTS

Trial characteristics: This study began enrolling subjects on April 04, 2007. The last patient completed the study on October 15, 2007. The study was conducted at one center in Boise, Idaho, USA. A total of 60 patients were enrolled; 53 completed the study.

Summary table for study OX22-007

Design	Single-center, OPEN LABEL, Chronic insomnia subjects
Duration	Multiple dose 60-day study
Dose	Zolpidem tartrate sublingual tablet (10mg OX 22)
Number Randomized	60 (Male:20 Female: 40)
Number Completing	**53** (88.3%)
Withdrawn • Patient wished to Discontinue • Unacceptable AE + lab value • Non-compliant with protocol	7 (11.7%) 2 (3.3%) 4 (6.7%) 1 (1.7%)

The patient Demographics and baseline characteristics are listed below.

Randomised (n)	**60**
Sex	
• Female (n)	40 (33.3%)
• Male (n)	20 (66.7%)
Age	**Mean age (range)**
• Female	45 (26-63)
• Male	45 (21-64)
• All	45 (21-64)
Body Mass Index (kg/m2)	
• Female	29.2 (19.9 - 55.7)
• Male	28.7 (20.7 - 38.6)
• All	29.0 (19.9 - 55.7)
Height (cm)	
• Female	165.2 (152.5 - 181.5)
• Male	177.7 (167.5 - 186.0)
• All	169.4 (152.5 - 186.0)
Weight (kg)	83.0 (58.4 - 148.1)
Life style	
• Smokers (n)	0
• Consumers of xanthine-containing beverages (coffee or cola) (n)	12
• Positive drug screen (n)	0
• Positive serology (n)	0

Non-compliance with protocol and deviations:

- Patient 015 documented that, on 2 different nights, (dosing nights 34 and 36) her spouse informed her that she got up in the middle of the night (at 2am and 3am) and took another Zolpidem tartrate sublingual tablet. There were no other occurences following this episode. These occurrences were recorded as an AE - mild parasomnia, which was considered related to study medication by the sponsor and resolved without treatment.

Discontinued patients/Study withdrawal (N=7):

- **Patient 002 withdrew** from the study on day 43/60 after 37 doses (time to onset 765.50 hours) because of unacceptable adverse event due to "mild intermittent palpitations" while on study medication without experiencing other cardiovascular or ECG changes.
- **Patient 025 voluntarily withdrew** after having taken one tablet on day 1 of study. The subject concomitantly took Tylenol PM and experienced hallucinations, somnolence, nausea, and dysequilibrium.
- **Patient 039 was considered lost to follow-up and subsequently withdrawn** from the study when he did not return for follow up visits. "He was a 57-year old white male, experience an AE of intervertebral disc protrusion on 28 May 2007 that the investigator deemed was severe in intensity, unrelated to study drug, and was a serious adverse event requiring a 2-day (patient reported) hospital stay. The patient reported that he was admitted to the hospital with one ruptured disc and ruptured a second disc in his lower back while in the hospital. The subject stated that he was given oxycodone for pain and placed on bed rest at home. After repeated attempts by the clinic to contact the patient, the patient was considered lost to follow-up. The patient had reported taking 5 Zolpidem tartrate sublingual tablets during the 5 days prior to his hospitalization and was subsequently withdrawn from the study."
- **Patient 040** took 5 doses of Zolpidem tartrate sublingual tablets and experienced vertigo and disorientation by day 4. She described the product as "too strong of sleep aid for me." She discontinued medication and was **withdrawn from the study**.
- **Patient 053** missed a study visit, and missed more than 10 days of dosing with study medication. Subject was **withdrawn from study** on day 24 due to non-compliance.
- **Patient 054 was withdawn from the study** after 35 days on Zolpidem tartrate sublingual tablets because "patient wished to discontinue." There is no CRF attached.
- **Patient 060 withdrew from the study** on day 21/60 after 17 doses because of worsening headache and toothache from baseline. There was non-compliance during the study and complaints that the tablet "would not dissolve completely."

Summary of Visit 6 Questionnaire (copied from the Sponsor's submission)

Question	Statistic	Summary Result
Time to Fall Asleep (minutes)	Number of Responses	59
	MEAN	17
	SD	12.1
	MIN	3
	MEDIAN	15
	MAX	70
Effect of OX22 on Sleep		
Very Satisfied	n (%)	39 (66.1%)
Somewhat Satisfied	n (%)	15 (25.4%)
Neither Satisfied nor Dissatisfied	n (%)	2 (3.4%)
Very Dissatisfied	n (%)	1 (1.7%)
Somewhat Dissatisfied	n (%)	2 (3.4%)
Tablet Taste		
Completely Tasteless	n (%)	1 (1.7%)
Agreeably Tasteless	n (%)	5 (8.5%)
Mainly Tasteless and Acceptable	n (%)	8 (13.6%)
Disagreeable but Acceptable	n (%)	36 (61.0%)
Unacceptable Taste	n (%)	9 (15.3%)
Tablet Handling Problems		
Yes	n (%)	2 (3.4%)
No	n (%)	57 (96.6%)
Use if Commercially Available		
Yes	n (%)	43 (72.9%)
No	n (%)	16 (27.1%)

6 Review of Efficacy

Efficacy Summary

b(4)

b(4)

I have summarized the results of clinical studies OX22-007 and OX22-002 in section 5.3.

6.1 Indication

The 505(b)(2) application is for a change in dosage form from oral tablet to sublingual tablet. Given the small size of the efficacy database, efficacy review is contained in section 5. Zolpidem tartrate sublingual tablets is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

7 Review of Safety

Safety Summary

There were no deaths reported during this clinical development program.

Serious Adverse Events (Explained further in Section 7.3.2)
There were three non fatal serious adverse events:

In study OX22-006, a 45 year old female took study drug (Ambien) before the serum HCG results were available and became aware that she was pregnant. She was discontinued from the study. She spontaneously aborted 2 weeks later. She was not on concomitant medications and without prior medical history of illness. The sponsor identified the SAE as possibly unrelated to study treatment and I agree with this conclusion.

In study OX22-007, a 57 year old male experienced ruptured intervertebral discs and hospitalized. His complaints began prior to study enrollment when he had recurrent back pain related to muscle spasms for which he had been on Flexeril 5mg daily. He was lost to follow up subsequently and it was considered unrelated to study medication by the sponsor. I agree that the AE was unlikely related to drug exposure as the patient had exacerbation of his ongoing symptoms.

A 64 year old old female with a past medical history significant for insomnia since 2004, asthma, transient dyspnea, migraine headaches and other headaches, and hot flashes started dosing on 4/20/2007. The sponsor identified that she experienced an unrelated serious adverse event of asthma exacerbation on [redacted] After treatment in the emergency room she recovered and continued on the study medication. I agree with the sponsors interpretation and that the AE was unlikely study drug related.

b(6)

Withdrawals
Across all studies, 12 subjects were withdrawn prior to completing the study. 5 subjects discontinued treatment because of an AE. Events that were possibly or probably related were headache, vertigo, disorientation, hallucinations, somnolence, balance disorder, nausea, palpitations, and fatigue. After review, the following AEs were unrelated: arthralgia, intervertebral disc protrusion, and pain. The treatment emergent adverse events were consistent and similar to the events reported in the Ambien label. No next-day residual effects on objective measures or subjective measures were seen. Only one subject had mild sublingual erythema after 35 doses that resolved before the next study visit. There were no other significant oral mucosal findings.

Except one subject, there were 4 healthy volunteers who experienced transiently elevated TSH levels during the study, which could probably have resulted from alteration in circadian rhytm. However, TSH levels were not measured in insomnia subjects. Abnormalities with thyroid hormone regulation is not an adverse event within the Ambien label.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

There were 7 clinical studies submitted with this NDA comparing Formulation I, Formulation II, and the Final Commercial Product (FCP) of OX22. Please refer to study details in section 5.1. Briefly, 5 studies were single-dose, cross over studies in healthy individuals. OX22-006 was the only double-blind, double-dummy, single dose, cross-over study that compared formulation II to Ambien® (zolpidem oral tablets [Sanofi-Aventis, US]) in patients with insomnia. None of the studies were placebo controlled trials. OX22-007 was a 60-day, multi-dose, open label, safety and tolerability study that evaluated the final commercial product (FCP). 2 PK studies compared formulation I to a product not approved by the FDA [Stilnoct® (Sanofi-Aventis, Europe)].

The Sponsor has provided a complete summary of all Treatment Emergent AEs in Table A.1 of the ISS. The ISS includes evaluation of adverse events rates from studies OX22-006 and OX22-007, and the rates were compared to the rates for events reported in the Ambien label.

Summary of Patient Disposition

Study	Treatment Groups (a)	Number of Randomized Subjects	Number of Treated Subjects (by treatment group)	Number of Completed Subjects
001	FI (5mg), FI (10mg), S	18	18, 18, 18,	18
002	FI (5mg), FI (10mg), S	21	19, 20, 20	18
004	FI (10mg), FII	12	12, 12	12
005	FII (fasting), FII (food), A	18	18, 18, 18	18
006	FII, A	73	72, 73	72
007	FCP	60	60	53
008	FII, FCP	19	18, 19	18

(a) FI=Formulation I, II=Formulation II (10 mg), FCP=Final Commercial Product (10 mg), S=Stilnoct® (10 mg), A= Ambien® (10 mg)

Copied from page 6 of 99, Module 5.3.5.3.2, Integrated Summary of Safety

Study OX22-001: Safety Overview and Adverse Events.

The sponsor reported no deaths, serious AEs, unexpected AEs or other significant AEs. There were 22 AEs that occurred in 9 subjects. Of these 9, 9, and 4 AEs occurred with treatments OX22 5 mg, OX22 10 mg, and Stilnoct 10 mg respectively. Most AEs were of mild intensity, there were five moderate and no severe AEs reported. The most frequently occurring AEs were dizziness (n=6), headache (n=3), nausea (n=3), double vision (n=2), vomiting (n=2) and common cold (n=2). The breakdown of these AEs using MedDRA (Version 9.1) by treatment has been summarized for all studies in a table that will be presented in section 9.5. Fourteen of the AEs were judged to be possibly or probably related to the study drug. One subject experienced three related AEs with two of the study medications (OX22 10 mg and Stilnoct). Three AEs occurred within 30 minutes of study drug administration (OX22 10 mg, subject #4, #5 and #11).

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Study OX22-002: Safety Overview and Adverse Events.

21 subjects were randomized. No subject withdrew due to an adverse event. 3 patients discontinued but they were included in the safety analysis set. The reasons for discontinuation is **copied from the Sponsor's submission below.** Subject no. 001 withdrew on P1D2 because of a mistake in administration: the sublingual tablet was swallowed as an oral tablet. Subject no. 007 withdrew on P3D1 because no valid nap was recorded throughout the periods. Subject 012 withdrew on P3D-1 due to lack of compliance according to the actimetry record.

Subject no.	Sex	Age	Last visit	Treatment received	Reason for discontinuation
1	female	25	2004-08-04	OX22 10 mg	Sublingual tablet swallowed
7	female	31	2004-08-31	Stilnoct 10 mg OX22 10 mg	No sleep recorded during nap
12	female	20	2004-09-21	OX22 5 mg Stilnoct 10 mg	Do not comply with actimetry schedule

The sponsor reported no deaths, serious AEs, unexpected AEs or other significant AEs. There were 24 AEs that occurred in 14/21 subjects as shown in the tables below. One AE occurred prior to study drug administration and 23 occurred during the treatment period. Of these 3, 10, and 10 AEs occurred with treatments Stilnoct® 10 mg, OX22 5 mg, and OX22 10 mg respectively. Eight (8) were considered not to be related to the study drug. Twelve of the AEs were of mild intensity (3 for Stilnoct® 10 mg, 4 for OX22 5 mg, 5 for OX22 10 mg) and 11 were moderate (6 for OX22 5 mg, 5 for OX22 10 mg). None of the AEs was of severe intensity. The most frequently occurring AEs were somnolence (5 episodes), headache (4 episodes; OX22 10 mg), and fatigue (4 episodes). The breakdown of these AEs using MedDRA (Version 9.1) by treatment has been summarized in the table below.

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Table 12 Summary of all AEs in the study

Body system (SOC) Preferred term (PT)	OX22 5 mg	OX22 10 mg	Stilnoct® 10 mg	Prior to study treatment
Body as a whole-general disorders				
Fatigue	2(R)	2(NR)	-	-
Headache	-	4 (1NR,3R)	-	-
Malaise	-	1(R)	-	-
Central and peripheral nervous system disorders				
Dizziness	-	-	1(R)	-
Gastrointestinal disorders				
Abdominal pain	-	-	-	1(NR)
Nausea	1(R)	-	-	-
Psychiatric disorders				
Mood disorder	1(NR)	-	-	-
Sleep disorder	1(R)	-	-	-
Somnolence	3(R)	1(R)	1(R)	-
Respiratory, thoracic and mediastinal disorders				
Rhinitis	-	1(NR)	-	-
Skin and appendages disorders				
Pruritus	1(R)	-	-	-
Rash erythematous	1(NR)	-	-	-
Rash maculo papular	-	-	1(NR)	-
Vascular (extracardiac) disorders				
Flushing	-	1(NR)	-	-
Total	10 (8R,2NR)	10(5R,5NR)	3(2R,1NR)	1(NR)

R: related to study drug
NR: not related to study drug

Study OX22-004: Safety Overview and Adverse Events.
The sponsor reported no deaths, serious AEs, unexpected AEs or other significant AEs. There were 14 AEs that occurred in 6 subjects. Of these 8 and 6 AEs occurred with optimized formulation II (composition A) and formulation I (composition B) respectively. Most AEs were of mild intensity, there were 2 moderate and no severe AEs reported. The most frequent occurring AE's were nausea (n=2), headache (n=2) and double vision (n=2). The breakdown of these AEs using MedDRA (Version 9.1) by treatment has been summarized for all studies in a table that will be presented in section 9.5. Nine of the AEs were judged to be possibly or probably related to the study drug.

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Study OX22-005: Safety Overview and Adverse Events.

The sponsor reported no deaths or serious AEs. There were 13 AEs that occurred in 6 subjects. 8 AEs in 4 subjects occurred with the administration of the test drug regardless of the condition (fast vs. fed) and 2 AEs in 2 subjects occurred with the administration of the RLD. 5 moderate AEs, 6 mild AEs, and 2 severe AEs were reported during the study. Subject 117 who had the 2 severe AEs, experienced severe diplopia and severe headache (lightheadedness) beginning 0.5 hour after administration of Ambien® fasting, which subsided 0.5 hour later. Both severe AEs were considered related to study medication.

Two AEs were considered unexpected. Subject 112 (Ambien® fasting) had mild serum TSH increased at the initial Screening Visit (4.6 mE/L, reference 0.4-3.5 mE/L), and was ongoing at the end of the study (5.1 mE/L). Subject 113 (OX22 with meal - initial Screening Visit 2.6 mE/L) had serum TSH increased at the end of the study (5.9 mE/L). Both of these unexpected AEs were considered not related to study medication by the investigator.

For all AEs, the relationship to the study treatment, as judged by the sponsor, was reported as probable for four events, possible for four and unlikely for five of the AEs. 9/13 AEs were resolved at study completion. 4 were still ongoing at the last study visit (Subject 105 - chest pain and hypoaesthesia, Subjects 112 and 113 - blood TSH increased). None of these ongoing AEs were considered to be related to the study treatment by the sponsor. The subjects were referred to a general practioner for further evaluation and there is no further information available on these subjects.

Subject 105: The sponsor used the preferred terms fatigue, chest pain and hypoaesthesia as non serious AEs of moderate intensity with unlikely causality due to drug for chest pain and hypoaesthesia, and fatigue possibly related to drug.

Subj No	Preferred Term*	Treatment	Time from dosing	Intensity	Serious	Causal relationship*
105	Fatigue	OX22 fasting	24.5 h	Moderate	No	Possible
105	Chest pain	OX22 meal	2 days, 11 h, 20 min	Moderate	No	Unlikely
105	Hypoaesthesia	OX22 meal	2 days, 11 h, 20 min	Moderate	No	Unlikely

Copied from page 32 of 50 OX22-005 study report, Table 6.

Reviewer: After reviewing the data with corresponding clinical and laboratory data I think Subject 105, 23 year old female experienced fatigue prior to and upto 24 hours after fasting dose of sublingual zolpidem. At baseline she had sinus bradycardia, and QTc 406msec. When she returned for 2nd period during the cross over study 2 days later she experienced chest pain that persisted during her subsequent/last visit when she experienced left arm hypoaesthesia (QTc=446msec) without other ECG findings. In addition, she had transient elevation of TSH levels that returned to baseline at final visit. She had no pre-exisiting medical conditions listed and she took acetaminophen when she experienced chest pain. Given the lack of significant ECG findings and unchanged vital signs from baseline it was unlikely due to the drug.

The most frequently occurring AEs were headache (n=3), elevated TSH (n=4) and nausea (n=2), which were reported for both OX22 and Ambien® treatment. The breakdown of these AEs using MedDRA (Version 9.1) by treatment has been summarized for all studies in a table that will be presented in section 9.5. Eight of the AEs were judged to be possibly or probably related to the study drug.

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

AE System Organ Class and Perferred Term*	OX22 with meal Treatment-Emergent (Treatment-Related)	OX22 fasting Treatment-Emergent (Treatment-Related)	Ambien® fasting Treatment-Emergent (Treatment-Related)
Eye Disorders	0	0	1 (1)
Diplopia	0	0	1 (1)
Gastrointestinal Disorders	1 (1)	0	1 (1)
Nausea	1 (1)	0	1 (1)
General Disorders and Administration Site Conditions	1 (0)	1 (1)	0
Chest pain	1 (0)	0	0
Fatigue	0	1 (1)	0
Infections and Infestations	1 (0)	0	0
Nasopharyngitis	1 (0)	0	0
Investigations	1 (0)	0	1 (0)
Blood thyroid stimulating hormone increased	1 (0)	0	1 (0)
Nervous System Disorders	2 (1)	1 (1)	2 (2)
Dizziness	1 (1)	0	0
Headache	0	1 (1)	2 (2)
Hypoaesthesia	1 (0)	0	0
Total	**6 (2)**	**2 (2)**	**5 (4)**

* MedDRA v. 9.1
Copied from page 31 of 50, Module 5.3.1.2.3, Clinical Study Report OX22-005

Study OX22-006: Safety Overview and Adverse Events.
The sponsor reported no deaths in this study. The breakdown of these AEs were done using MedDRA (Version 9.1) by treatment. The frequency of AEs were analyzed and coded from the LLT to PT and SOC by pooled centers, and for individual centers by the sponsor.

There were 31 AEs that occurred in 24 subjects as shown in the table below. 18 AEs in 16 subjects occurred with the administration of Ambien® and 13 AEs in 11 subjects occurred with the administration of OX22 (Formulation II).

7 moderate AEs, and 23 mild AEs were reported during the study. Subject 701-003 had 2 Serious AEs (pregnancy and miscarriage) who discontinued the study due to pregnancy and later had a miscarriage. The pregnancy started before treatment was initiated but was not discovered until after the patient had received treatment with Ambien®. She discontinued after study period 1.

For all AEs, the relationship to the study treatment, as judged by the sponsor, was reported as probable or possible for 22 AEs (12/18 for Ambien and 10/13 for OX22). 10 AEs were considered related to OX22 and 12 AEs were considered related to Ambien®. There were no ongoing AEs at study completion that required further follow up and the outcome for all AEs was "recovered". **The most frequently occurring AEs were somnolence (5 adverse events in 4** patients [5.5%]), nausea (4 adverse events in 4 patients [5.5%]), dysgeusia (4 adverse events in 3 patients [4.1%]) and dizziness (3 adverse events in 2 patients [2.7%]), which were reported for both OX22 and Ambien® treatment. The SOC with most frequent AEs was Nervous system disorders (Ambien treatment = 6; OX22 treatment = 5) and Gastrointestinal disorders (Ambien treatment = 6; OX22 treatment = 2).

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Adverse events by treatment, system organ class and preferred term; Study OX22-006

System organ class Preferred term	Ambien* (n=73) nae (n, %)	OX22 (n=72) nae (n, %)
Nervous system disorders	**6 (6, 8.2%)**	**5 (4, 5.6%)**
Somnolence	2 (2, 2.7%)	3 (3, 4.2%)
Dizziness	2 (2, 2.7%)	1 (1, 1.4%)
Headache	---------	1 (1, 1.4%)
Hypersomnia	1 (1, 1.4%)	---------
Migraine	1 (1, 1.4%)	---------
Gastrointestinal disorders	**6 (6, 8.2%)**	**2 (2, 2.8%)**
Dysgeusia	2 (2, 2.7%)	2 (2, 2.8%)
Nausea	4 (4, 5.5%)	---------
Respiratory, thoracic and mediastinal disorders	**3 (2, 2.7%)**	---------
Bronchitis acute	1 (1, 1.4%)	---------
Respiratory disorder	1 (1, 1.4%)	---------
Rhinitis allergic	1 (1, 1.4%)	---------
Infections and infestations	**1 (1, 1.4%)**	**1 (1, 1.4%)**
Influenza	1 (1, 1.4%)	1 (1, 1.4%)
Pregnancy, puerperium and perinatal conditions	**1 (1, 1.4%)**	---------
Abortion spontaneous	1 (1, 1.4%)	---------
Pregnancy	---------	---------
Cardiac disorders	---------	**1 (1, 1.4%)**
Sinus bradycardia	---------	1 (1, 1.4%)
General disorders and administration site conditions	**1 (1, 1.4%)**	---------
Asthenia	1 (1, 1.4%)	---------
Metabolism and nutrition disorders	---------	**1 (1, 1.4%)**
Iron deficiency anemia	---------	1 (1, 1.4%)
Musculoskeletal and connective tissue disorders	---------	**1 (1, 1.4%)**
Hypotonia	---------	1 (1, 1.4%)
Psychiatric disorders	---------	**1 (1, 1.4%)**
Nightmare	---------	1 (1, 1.4%)
Skin and subcutaneous disorders	---------	**1 (1, 1.4%)**
Erythema	---------	1 (1, 1.4%)

Copied from page 65 of 434, Module 5.3.5.1.3, Clinical Study Report OX22-006

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

The results of the next day residual effects between OX22 and Ambien did not show any difference.

Narratives of SAE: Patient No. 701-003 [Pregnancy]

"This 45-old female was randomized on 16 May 2007 and received the first study drug on 17 May 2007. No relevant medical history was recorded. The last menstruation was on ——— '. At the randomization visit, on Day -1 of Period 1 (———), urine pregnancy test performed at site was negative, but serum pregnancy test performed by the central lab ——

b(6)

was positive. The patient was subsequently withdrawn from the study. A serum retest was performed on and was positive. On the patient presented metrorrhagia and a miscarriage was diagnosed. No ultrasonic procedure was performed and the patient did not visit the gynecologist. A serum beta hCG test performed **was negative. The patient was in a good condition."** b(6)

Study OX22-007: Safety Overview and Adverse Events.
The sponsor reported no deaths in this study. The breakdown of these AEs were done using MedDRA (Version 9.1) by treatment. The frequency of AEs were analyzed and coded from the LLT to PT and SOC.
The study subjects took an average of 55.3 doses of the Investigational medical product for mean duration of 56 days with compliance rate of 98.8%. Details regarding discontinued patients, study withdrawal (N=7), non-compliance with protocol, and protocol deviations have been discussed in the above paragraphs.

There were 72 AEs that occurred in 34 (56.7%) subjects. 19 moderate AEs were reported by 13 (21.7%) patients, and 52 mild AEs were reported by 29 (48.3%) patients during the study. One severe AE was reported by 1 patient. Overall, there were 2 SAEs in 2 patients (3.3%). Patient 039 experienced the SAE of severe intervertebral disc protrusion and patient 017 experienced asthma exacerbation with tachycardia. They were considered unrelated to study medication by the investigator and it is detailed in in section 7.3. There was a single instance of mild sublingual erythema reported in one patient at one study visit.

For all AEs, the relationship to the study treatment, as judged by the investigator, was reported as probable or possible for 43 AEs reported by 27/72 patients. Out of the 7 patients who withdrew from the study, 5 withdrew because of (12) AEs. There were no ongoing AEs at study completion that required further follow up and **the outcome for all AEs was "recovered". The** most frequently occurring AEs were somnolence (8 adverse events in 8 patients [13.3%]), fatigue (5 adverse events in 4 patients [6.7%]), dizziness (4 adverse events in 4 patients [6.7%]), headache (4 adverse events in 4 patients [6.7%]), nausea (3 adverse events in 3 patients [5.0%]), and balance disorder (3 adverse events in 3 patients [5.0%]). The SOC with most frequent AEs was Nervous system disorders and Gastrointestinal disorders.

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Study OX22-008: Safety Overview and Adverse Events.
The sponsor reported no deaths, serious AEs, unexpected AEs or other significant AEs. There were 39 AEs that occurred in 13 subjects as shown in the tables below. 13 AEs in 7 subjects occurred with the administration of formulation II and 26 AEs in 11 subjects occurred with the administration of FCP-Zolpidem tartrate sublingual tablets. 8 moderate AEs (6 of these 8 AEs are counted from one subject, Subject 114, who experienced 6 episodes of intermittent vomiting) and 31 mild AEs were reported during the study.

6 of the AEs were judged to be possibly related, 23 AEs probably related to the study drug and unlikely for 10 of the AEs. All AEs resolved by the end of the study, with 3 exceptions. Subject 104 had mild dysuria that was considered unrelated to the study medication, 38 h and 51 min. following administration with FCP in Period 2. Subject 105 had mild stomach flu that was considered unrelated to the study medication, 31 h and 18 min. following administration of FCP in Period 2. Subject 110 had mild nasopharyngitis that was considered unrelated to the study medication, 11 h and 33 min. following administration of FCP in Period 2.

The most frequently occurring AEs for both formulations were dizziness (n = 10) and nausea (n = 5). The breakdown of these AEs using MedDRA (Version 9.1) by treatment has been summarized for all studies in a table that will be presented in section 9.5.

Clinical labs, vital signs, physical findings and ECG results will be summarized in section 7.3.

Table 15 Frequencies of All AEs Coded by MedDRA (SOC, Preferred term and Lower level term) for Formulation II and FCP

System Organ Class (SOC)	Preferred term	Lower level term	Formulation II (N=18)	Final Commercial Product (FCP) (N=19)	Overall (N=19)
Eye disorders	Eye pain	Pain in eyes	1	1	2
	Vision blurred	Difficulty focusing eyes	1	1	2
Gastrointestinal disorders	Dry mouth	Dry mouth	1		1
	Nausea	Nausea	2	3	5
	Vomiting	Vomiting		6	6
General disorders and administration site conditions	Fatigue	Fatigue		2	2
Infections and infestations	Gastroenteritis viral	Stomach flu		1	1
	Nasopharyngitis	Common cold		1	1
Musculoskeletal and connective tissue disorders	Sensation of heaviness	Heaviness in limbs	1		1
		Sensation of heaviness	1		1
Nervous system disorders	Coordination abnormal	Coordination impaired		1	1
	Dizziness	Dizziness	4	6	10
	Headache	Headache	2	1	3
	Hypoaesthesia	Numbness in hand		1	1
Renal and urinary disorders	Dysuria	Dysuria		1	1
Respiratory, thoracic and mediastinal disorders	Epistaxis	Epistaxis		1	1
	Total				39

Adverse events can be counted multiple times with the same lower level term on the same subject Date created: October 18, 2007 Path: N:\Project\Q-27196\Report\tables\Tab09.sas

7.1.2 Adequacy of Patient Exposure and Safety Assessments

A total of 201 subjects were randomized to OX22 10 mg (FI, FII, or FCP). This included 88 healthy adult subjects (single doses in Studies 001, 002, 004, 005, and 008) and 113 adult chronic insomnia patients (73 subjects with single doses in Study OX22-006 and 60 subjects with once daily dosing for approximately two months in Study OX22-007). The extent of exposure for all the single dose studies (including the double-blind study OX22-006) and the

multiple dose study OX22-007 is shown below. In OX22-007 study, the subjects took an average of 55.3 doses of the Investigational medical product for mean duration of 56 days with compliance rate of 98.8%. Individual study details are described in section 5.3.

Summary of Extent of Exposure (All treated subjects)

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 5 mg (FI) (N=37)	OX22 10 mg (FI) (N=50)	OX22 10 mg (FII, Fasting) (N=120)	OX22 10 mg (FII, Food) (N=18)	OX22 10 mg (FCP) (N=79)	Stilnoct® 10 mg (N=38)	Ambien® 10 mg (N=91)
Number of Days of Dosing (Single Dose Studies)	n	37	51	120	18	19	38	91
	Mean	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Range	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1
Number of Days of Dosing (Multiple Dose Study 007)	n					60		
	Mean					56.4		
	SD					15.96		
	Median					61.0		
	Range					1 - 68		

Copied from Table 3.1, page 21 of 99, Module 5.3.5.3.2, Integrated Summary of Safety

Summary of Extent of Exposure
(All Treated Subjects – Double-Blind Studies)

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 10 mg (FII, Fasting) (N=72)	Ambien® 10 mg (N=73)
Number of Days of Dosing (Single Dose Studies)	n	72	73
	Mean	1.0	1.0
	SD	0.00	0.00
	Median	1.0	1.0
	Range	1 - 1	1 - 1

The Ambien treatment group was also fasting; both treatment groups had the same fasting requirements.
Copied from Table 3.2, page 21 of 99, Module 5.3.5.3.2, Integrated Summary of Safety

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The database consisted of a small number of generally brief PK and PD studies of varying design, so safety was not pooled across studies. The Sponsor provided a complete combined summary of all AEs in Table A.1, page 40 of 99 of the ISS. The AEs were coded using MedDRA Version 9.1.

Tha safety data for the individual studies has been presented in section 5.3.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Although the safety dataset contain different formulations, relevance is given to Formulation II, FCP, and Ambien. No direct study comparison was made between Ambien and the FCP, which the sponsor intends to market. However, Ambien was compared to Formulation II and a PK/BE bridging study was conducted comparing Formulation II to FCP. A single local oral toxicity study was conducted with the FCP.

Subjects were predominantly white (>95%) aged 18-64 years, F>M.

Summary of Demographic Characteristics (All treated Subjects)

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 5 mg (FI) (N=37)	OX22 10 mg (FI) (N=50)	OX22 10 mg (FII, Fasting) (N=120)	OX22 10 mg (FII, Food) (N=18)	OX22 10 mg (FCP) (N=79)	Stilnoct® 10 mg (N=38)	Ambien® 10 mg (N=91)
Age	Mean	25.2	25.6	34.7	24.4	40.7	25.4	37.6
	SD	5.16	4.71	12.01	3.76	13.63	5.17	12.06
	Median	25.0	25.0	33.0	23.5	41.0	25.0	39.0
	Range	18 - 39	18 - 39	18 - 63	21 - 38	18 - 64	18 - 39	19 - 63
Gender	Male (n,%)	12 (32.4%)	20 (40.0%)	57 (47.5%)	12 (66.7%)	27 (34.2%)	12 (31.6%)	43 (47.3.
	Female (n,%)	25 (67.6%)	30 (60.0%)	63 (52.5%)	6 (33.3%)	52 (65.8%)	26 (68.4%)	48 (52.7%)
Race	WHITE	18 (100.0%)	30 (100.0%)	119 (99.2%)	18 (100.0%)	76 (96.2%)	18 (100.0%)	91 (100.0%)
	BLACK OR AFRICAN AMERICAN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
	OTHER: AMERICAN INDIAN 1/64	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
	OTHER	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Unknown *	19	20	0	0	0	20	0
Weight(lbs)	Mean	149.4	149.9	153.7	154.1	174.9	148.6	154.0
	SD	27.64	26.68	23.10	19.30	40.43	27.64	23.52
	Median	152.1	150.5	152.1	153.2	163.1	148.8	152.1
	Range	108 - 213	108 - 213	91 - 227	123 - 187	112 - 327	108 - 213	91 - 227
Height(in)	Mean	68.1	68.3	67.5	69.4	67.0	67.9	67.2
	SD	3.86	3.85	3.59	3.61	3.27	3.91	3.68
	Median	66.9	67.7	66.9	68.5	66.6	66.9	66.1
	Range	62 - 76	62 - 76	60 - 78	65 - 78	60 - 73	62 - 76	60 - 78

*Race was not collected for Study 002

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 10 mg (FII, Fasting) (N=72)	Ambien® 10 mg (N=73)
Age	Mean	40.8	40.8
	SD	11.22	11.15
	Median	41.0	41.0
	Range	19 - 63	19 - 63
Gender	Male (n,%)	31 (43.1%)	31 (42.5%)
	Female (n,%)	41 (56.9%)	42 (57.5%)
Race	WHITE	72 (100.0%)	73 (100.0%)
Weight(lbs)	Mean	154.1	154.0
	SD	24.70	24.57
	Median	152.1	152.1
	Range	91 - 227	91 - 227
Height(in)	Mean	66.6	66.6
	SD	3.52	3.51
	Median	66.1	66.1
	Range	60 - 76	60 - 76

Copied from Table 2.1 and Table 2.2, pages 19 & 20 of 99, Module 5.3.5.3.2, Integrated Summary of Safety

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The methods that the Sponsor used for routine clinical testing were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The information on zolpidem tartrate metabolism, clearance and drug-drug interaction comes primarily from pre- and post-marketing experience with Ambien®. The currently approved Ambein label contains information on the enzymatic pathways responsible for drug clearance.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The class specific adverse events of concern are the next-day residual effects, rebound effect after abrupt drug discontinuation, and behavioral changes. As a basis for this 505(b)(2) NDA

application the Sponsor relies on single-dose bridging PK/BA studies with the RLD, and a single-dose study to compare the pharmacodynamic effects between the the sublingual and the oral formulation. The effect of drug withdrawal, rebound, dose-relationship of adverse events were not determined and they rely on the information already in the Ambien label. There was one study, OX22-006 that assessed next-day residual effects and there was no difference in effect seen between the oral and sublingual formulation.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the studies done in support of this application.

7.3.2 Nonfatal Serious Adverse Events

[*Reviewer's note: The data used for this section consists of the Sponsor's narrative summaries, line listings and case report forms. The relevant AE are highlighted with bold font.*]

Study OX22-006: Subject 701-003, Ambien treatment arm: The subject, a 45 year old female presented for study drug dosing on 5/17/07. The serum HCG result was still pending and a urine pregnancy test was obtained which was negative. The subject then took a single dose of Ambien on 5/17/2007. Her serum pregnancy test from ——— came back as positive on ———. The subject was then discontinued from the study. A retest on ——— **confirmed a positive serum pregnancy test.** On ——— she experienced an unrelated serious adverse event of **spontaneous abortion (miscarriage)** with metrorrhagia which ended ———. Repeat HCG ——— was negative. Ultrasonic procedure was not performed. The subject recovered from this event but did not complete the study. The reporting study physician assessed the event as unlikely related to study medication. b(6)

Reviewer: I agree that the event was unlikely related to study medication. In the Ambien label or in the literature there is no report of miscarriage or abortion, and there is lack of data from controlled studies. There is a published case-report documenting the presence of zolpidem in human umbilical cord blood and regarding teratogencity from animal data. However, with this data it is inconclusive that approximately ten days after exposure to single drug dose in the mid menstrual cycle, the subject miscarried.

Study OX22-007: Subject 039, OX22 FCP: The subject, a 57 year old male with a past medical history significant for insomnia since 2004, generalized muscle aches, and muscle spasm started dosing on 5/23/2007 and experienced an **unrelated serious adverse event of two ruptured intervertebral discs in his lower back** on ———. His complaints began prior to study enrollment when he had recurrent back pain related to muscle spasms for which he had been on Flexeril 5mg daily. The subject stated that he was admitted to the hospital with one ruptured disc and had ruptured the second while in the hospital. He spent two days in the hospital, was prescribed Oxycodone for pain, and was placed on bed rest at home. The study drug was b(6)

withdrawn during hospitalization and the subject did not complete the study. After two attempts to contact the subject, the subject returned calls on 6/26/2007 stating that he was still on bed rest and has not made contact with hospital for records. He did not know which discs were ruptured, but stated the location of the discs were in his lower back. The site attempted to contact subject for follow-up 6/05/1007, 6/12/2007, and 6/19/2007 with no returned calls. On 6/20/2007, a certified letter was sent out to the subject with a request for contact. In addition, a medical release form and prepaid envelope for signed release and return of study medication was enclosed with the certified letter. On 6/31/2007 the certified letter was delivered and return receipt was subsequently signed by subject. The subject did not return medical release or study medication, nor did he contact the site for follow-up. He was lost to follow up subsequently and it was considered unrelated to study medication by the sponsor.
Reviewer: The information suggests that the subject suffered from low back pain prior to study drug initiation and then 5 days into therapy he experienced an exacerbation of the AE, for which he had been hospitalized. Since the subject did not cooperate for further information to know what cause the injury, it can be concluded that the AE was unlikely related to drug exposure as the patient had exacerbation of his ongoing symptoms.

Study OX22-007: Subject 017, OX22 FCP: The subject, a 64 year old female with a past medical history significant for insomnia since 2004, asthma, transient dyspnea, migraine headaches and other headaches, and hot flashes started dosing on 4/20/2007 and experienced an **unrelated serious adverse event of asthma exacerbation** (. Subject reported to the local emergency room (ER) at 2100 hrs. She complained of difficulty breathing and chest heaviness for the past two hours. Vital signs were significant for tachycardia, with a heart rate of 162 and a fever with a temperature of 100°F. The pulse then spontaneously dropped to 105-100 without treatment. The electrocardiogram demonstrated 1mm ST depression which improved with a decreased in the heart rate. A chest x-ray was obtained which showed no evidence of disease. The subject was admitted to the hospital . Both a computerized axial tomography (CT) and a lower extremity venous duplex study were obtained to evaluate the possibility of pulmonary embolus and were negative. A thyroid panel was within normal limits. The medical team suspected the subject ingested too much beta-agonist from too frequent use of the albuterol inhaler. On the subject was discharged from the hospital and instructed to follow up with her primary physician. No additional therapies were prescribed other than to decrease the albuterol to no more than 2 puffs q4hrs PRN. The medical impression was asthma exacerbation with tachycardia, due to over use of albuterol inhaler and that the adverse event was not study drug related. The subject recovered from this event, no action was taken with respect to study medication, and the subject completed the study. b(6)
Reviewer: I agree with the sponsor's findings. Cardiotoxicity is a known side effect of beta agonist therapy and the subject was hospitalized secondary to asthma exacerbation. Although bronchospasm is listed as a rare AE experienced on exposure to zolpidem, it is unlikely the subject had an isolated episode given past medical history of asthma. It is possible zolpidem may have caused drug interaction with albuterol. However given the episodic nature of this AE occurrence and symptoms dissipation upon hospital discharge following which the patient completed the study period, the adverse event was unlikely study drug related.

7.3.3 Dropouts and/or Discontinuations

Across all studies, *12 subjects* were withdrawn prior to completing the study.

5 subjects discontinued treatment because of an AE. According to the sponsor events that were possibly or probably related were headache, vertigo, disorientation, hallucinations, somnolence, balance disorder, nausea, palpitations, and fatigue. Events that were unrelated were arthralgia, intervertebral disc protrusion, and pain. As discussed in previous paragraphs, I agree that the AEs were unlikely study drug related.

Study OX22-002 (Formulation I compared to non-FDA approved drug): 3 patients discontinued but they were included in the safety analysis set. 21 subjects were randomized. No subject withdrew due to an adverse event. The reasons for discontinuation is copied from the Sponsor's submission. Subject no. 001 *withdrew* on P1D2 because of a mistake in administration: the sublingual tablet was swallowed as an oral tablet. She was replaced with subject 101. Subject no. 007 *withdrew* on P3D1 because no valid nap was recorded throughout the periods. She was replaced with subject 107. Subject 012 *withdrew* on P3D-1 due to lack of compliance according to the actimetry record and was replaced with subject 112. *The submission did not contain further details regarding these patients.*

Subject no.	Sex	Age	Last visit	Treatment received	Reason for discontinuation
1	female	25	2004-08-04	OX22 10 mg	Sublingual tablet swallowed
7	female	31	2004-08-31	Stilnoct 10 mg OX22 10 mg	No sleep recorded during nap
12	female	20	2004-09-21	OX22 5 mg Stilnoct 10 mg	Do not comply with actimetry schedule

Study OX22-007 (repeat-dose sublingual tolerability study of FCP): 7 patients discontinued

- Patient 002 *withdrew* from the study on day 43/60 after 37 doses (time to onset 765.50 hours) because of **unacceptable adverse event due to "mild intermittent palpitations"** while on study medication. Tachycardia (infrequent) and palpitations (controlled-trial incidence of atleast 1%) are AEs known to occur in the zolpidem drug exposed population. The subject experienced the AE likely due to drug exposure, however it cannot be concluded whether the subjects probability was higher due to the sublingual formulation.
- Patient 025 *voluntarily withdrew* after having taken one tablet on day 1 of study. The subject concomitantly took Tylenol PM and experienced **hallucinations, somnolence, nausea, and dysequilibrium**. The prior concomitant medication by it self may cause somnolence and dysequilibrium. However, an additive effect or interaction cannot be excluded that may have caused hallucinations (<1% incidence in controlled clinical trials with zolpidem) and nausea. It is likely that the subject withdrew due to drug exposure.
- Patient 039 Intervertebral disc protrusion, see discussion under SAE section 7.3.2.

- Patient 040 took 5 doses of Zolpidem tartrate sublingual tablets and experienced **vertigo and disorientation by day 4. She described the product as "too strong of sleep aid for me." She discontinued** medication and was *withdrawn* from the study. Both AEs are frequently seen in patients exposed to zolpidem as reported in the Ambien label. It cannot be concluded whether the sublingual formulation acted differently from the available information.
- Patient 053 missed a study visit, and missed more than 10 days of dosing with study medication. Subject was *withdrawn from study* on day 24 due to non-compliance.
- Patient 054 was *withdawn from the study* after 35 days on Zolpidem tartrate sublingual **tablets because "patient wished to discontinue." There is no CRF attached.**
- Patient 060 *withdrew from the study* on day 21/60 after 17 doses because of worsening headache and toothache from baseline. There was non-compliance during the study and **complaints that the tablet "would not dissolve completely." I did not find any other** reports of the tablet not dissolving, and neither have there be any reported concerns with dissolution.

Study OX22-006 (Formulation II compared to Ambien): 3 patients discontinued

- Patient 701-003: pregnancy and miscarriage while on Ambien arm of the study as detailed above in section 7.3.2.
- 322-005 and 703-002: Had major protocol deviations since they did not meet polysomnogram criteria; recordings were not initiated immediately following administering the investigational product.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AE results are discussed in detail under discussion of individual studies, section 5.3. The Sponsor discussed event rates for study OX22-007 comparing the Final Commercial Product to rates in the Ambien® label, and event rates for study OX22-006 that compared formulation II to Ambien in a single-dose cross-over study. In addition they provided overall treatment emergent AEs in the OX22 clinical development program.

In section 5.3.1 I have detailed the differences in the formulations and the clinical studies the sponsor submitted. The FCP is the intended product for marketing. FCP was not compared to Ambien. In stead the comparison was made to Formulation II and bridging studies were done between FCP and F II.

Eliciting AE data in the development program.
During the phase I trials, subjects were assessed at screening and during the course of the trial for AEs.

In study OX22-006, subjects were assessed at screening and at each visit during the course of the trial for adverse events. They were also assessed 7-10 days after final study drug administration at the final follow-up visit.

In study OX22-007, the subjects had a pre-study visit (approximately 11-14 days prior to baseline visit), baseline visit (visit 2), and four other study site visits (visits 3-6) for visual inspection of the oral cavity and for completing a questionnaire regarding the treatment of IMP. 10-14 days after study conclusion there was a post-study follow-up phone call.

Appropriateness of AEs categorization and preferred terms.
After reviewing the data tables for adverse events for verbatim terms and the assigned preferred terms the AEs appear to be appropriately categorized.

Summary of adverse events rates (All treated subjects)
The adverse events were coded using MedDRA Version 9.1. An overview of the rates of treatment-emergent adverse events are shown in table 4.1 below. 57% of subjects experienced at least one AE on the Final Commercial Product, and 40.5% of these subjects experienced possibly or probably related AE. *5 (6.3%) subjects discontinued from the study because of AE on the FCP that included headache, vertigo, disorientation, hallucinations, somnolence, balance disorder, nausea, palpitations, and fatigue.*

Number (%) of Subjects {tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}	OX22 5 mg (FI) (N=37)	OX22 10 mg (FI) (N=50)	OX22 10 mg (FII, Fasting) (N=120)	OX22 10 mg (FII, Food) (N=18)	OX22 10 mg (FCP) (N=79)	Stilnoct® 10 mg (N=38)	Ambien® 10 mg (N=91)
Any Adverse Event	12 (32.4)	17 (34.0)	25 (20.8)	4 (22.2)	45 (57.0)	5 (13.2)	19 (20.9)
Any Related* Adverse Event	9 (24.3)	12 (24.0)	22 (18.3)	1 (5.6)	32 (40.5)	4 (10.5)	13 (14.3)
Any Serious Adverse Event	0	0	0	0	2 (2.5)	0	1 (1.1)
Any Related* Serious Adverse Event	0	0	0	0	0	0	0
Any Adverse Event Leading to Disc.	0	0	0	0	5 (6.3)	0	0
Death	0	0	0	0	0	0	0

*Related includes any AEs with Relationship code of: unknown, possibly related, probably related, or related

Table 4.1, page 23 of 99 Integrated Summary of Safety.

In the table above, OX22 Final Commercial Product (FCP) group includes subjects that were enrolled in the 60-day dosing study (Study 007). All other treatment groups only received a single dose. The event rates of FCP therefore appear greater in number compared with other

treatment groups. A comparison of AEs across columns may give the appearance of higher AE rate in the FCP treated group.

In the following sections, discussions of FCP event rates are compared with the Ambien label, when comparative data was available.
Treatment Emergent Adverse Events: Please see Appendix 9.5 for detailed table. The study table was modified from Table A.1, Integrated Summary of Safety section 5.3.5.3.2 pages 40-44 of 99.

The most frequent adverse events were reported in the Nervous system disorder SOC followed by GI disorders SOC. On FCP 12.7% cases had dizziness; 10.1 % subjects had somnolence; headache 6.3%; balance disorder 3.8%; 3.8 % cases of paraesthesia.

6 (7.6%) subjects on FCP complained of fatigue, and it was also a reason for discontinuation from the study. Fatigue is a recognized side effect of sedative hypnotics. In long term placebo controlled studies cited in the Ambien® label, fatigue was reported by 1% of the subjects on Ambien® and 2 % taking placebo. In the Ambien® Controlled Release (CR) label, fatigue was reported by 3% of subjects taking Ambien® CR 12.5 mg and 2% of placebo. However, no direct comparison can be made to interpret results since there was no direct comparison made between products, and for the duration tested (FCP=60 days and Ambien=single dose).

Dizziness: was reported with the highest frequency across all OX22 formulations. 10 (12.7 %) cases appeared to be with the use of FCP (n=79). 86% of dizziness AEs were mild and 14% of moderate intensity. None of the patients discontinued. There were no reports of falls or injury related to this AE. In the double-blind study OX22-006 (N=73), the incidence of dizziness was similar for subjects taking both OX22 10 mg FII (1.4%) and Ambien 10 mg (2.7%). "In placebo-controlled trials referenced in the Ambien label dizziness on Ambien treatment was 1% in short term trials (10 nights at <=10 mg in patients with insomnia) and 5% in long term trials (35 nights at <=10 mg in patients with insomnia) though in other studies with Ambien, dizziness rates are reported to be a common adverse event." From the literature reviews provided by the Sponsor it appears that dizziness occurs frequently in healthy volunteers while given zolpidem tartrate. "In a post-marketing surveillance study that investigated the safety of zolpidem [administered as 5 mg, 10 mg, or 20 mg doses (or greater)] in 16,944 cases of patients with sleep disturbances, the most common AEs were nausea, dizziness, malaise, nightmares, agitation, and headache. There was no difference in the frequency of AE reporting between dose groups (Hajak and Bandelow, 1998)." Reviewer's comment: The AE is within the observed frequency of AEs observed with zolpidem and it des not appear to be higher than expected with the RLD formulation.

Somnolence: was also reported frequently across all OX22 formulations and 10.1% cases occurred with OX22 FCP (N=79). In the double-blind study OX22-006 (N=73), the incidence of somnolence was 4.2% for OX22 10 mg FII and 2.7% with Ambien 10 mg. In placebo-controlled trials referenced in the Ambien label if "drowsiness" was linked to PT for "somnolence", then on Ambien treatment the rate was 2% in short term trials (10 nights at <=10 mg in patients with insomnia) and 8% in long term trials (35 nights at <=10 mg in patients with insomnia) compared to placebo rate of 5%.

Headaches occurred in 6.3% of subjects taking OX22 10 mg FCP (N=79), and 3.3% subjects taking OX22 10 mg formulation II fasting. The incidence in the short term placebo controlled trials (10 nights at <=10 mg in patients with insomnia) in the Ambien label was 7% and occurred frequently (>1/100).

Gastrointestinal SOC: The incidence of nausea was 6.6% on FCP. The rate of nausea with Ambien in controlled studie was 0.1%-1.0% in the Ambien® label. However, the Sponsor reported the rate of nausea in page 8 of the ISS as "similar to those seen in the Ambien® label: nausea (6.0%) and vomiting (1.0%); these rates were reported to be equal to those of placebo." In the double-blind study OX22-006, rates of these adverse events were 0% for OX22 10 mg, FII and 5.5% for Ambien® 10 mg. Vomiting rates were 2.5% with FCP as compared to <0.1% in the Ambien label.

According to the sponsor psychiatric disorder adverse events were uncommon in the OX22 development program. In the OX22 FCP group (N=79), the most frequently occurring event was parasomnia (2.5%). Depressed mood occurred in one subject (1.3%) on FCP. No subjects reported suicidal ideation or a suicide attempt. Other psychiatric disorder events that each occurred in only one subject included agitation, disorientation, hallucination, and nervousness. In published literature, studies with Ambien reported psychiatric disorders. Episodes of hallucinations (auditory, visual and tactile) were detailed in 20 case reports. Virtually all reports were in subjects that took 5 to 20 mg zolpidem tartrate oral tablets. As described in the Ambien® label, in controlled trials, < 1% of adults with insomnia who received zolpidem reported hallucinations. However, in a pediatric clinical trial, 7.4% patients with insomnia and ADHD reported hallucinations.

Next day residual effects were assessed in study OX22-006 comparing formulation II to Ambien® in a double blind single-dose cross over study by the following Neurocognitive tests: Leeds psychomotor tests (Critical Flicker Fusion Test, Multiple Choice Reaction Time), Bond & Lader Visual Analogue Scale (VAS) and Digit Symbol Substitution Test (DSST). The results of the next day residual effects between OX22 and Ambien did not show any difference. Minimal next day residual effects have been observed in published literature with zolpidem tartrate oral tablets. The Ambien label has described studies pertinient to safety concerns for the sedative/hypnotic class that will be used in the OX22, Zolpidem tartrate sublingual tablets label as well.

ORAL EXAMS: Local tolerability of OX22 FCP was evaluated only in study OX22-007 (N=60) for 60 days. The sublingual mucosa was investigated 5 times during the study by the investigator. One subject (out of 60) had sublingual erythema noted after 35 doses. The erythema was described as mild and <2mm; it resolved prior to the next study visit. The Sponsor reported that no other subjects had sublingual erythema. I searched for other possible "objective signs" with related terms that can be associated with lesions of the oro-buccal mucosal cavity. Sublingual "erythema" was coded to skin and subcutaneous tissue disorders SOC, and I think it should have been appropriately coded to gastrointestinal disorders SOC since this is "oral mucosal erythema". One patient experienced "transient paresthesia of tongue" as the only AE after 33 doses, which resolved in 2 days. It was appropriately coded to the gastrointestinal

disorders SOC. There was a case of canker sore in another patient after 35 doses which resolved in 4 days (LLT) → aphthous stomatitis (PT) → appropriately coded to the gastrointestinal disorders SOC. Glossitis was an AE in one individual that started on day 12 and resolved by day 43, which was in the GI SOC. It appears that if the above 4 AEs were combined as an oro-buccal mucosal cavity event, the rate would be 6.7%. There are no comparative estimates for this drug. But based on AE rates from the oral toxicity study I think the AEs can be monitored and reversed upon discontinuation of the drug. In spite of the subjective responses from the participants at the end of the study regarding taste (disagreeable or unacceptable tatse 76%), there was high acceptability and satisfaction among study participants that they would continue to use if commercially available.

Chest pain was reported by one subject (OX22-005) in the OX22 10 mg FII, food group (1/18 = 5.6%). After reviewing the data with corresponding clinical and laboratory data I think Subject 105, 23 year old female experienced fatigue prior to and upto 24 hours after fasting dose of sublingual zolpidem. At baseline she had sinus bradycardia, and QTc 406msec. When she returned for 2nd period during the cross over study 2 days later she experienced chest pain that persisted during her subsequent/last visit when she experienced left arm hypoaesthesia (QTc=446msec) without other ECG findings. In addition, she had transient elevation of TSH levels that returned to baseline at final visit. She had no pre-exisiting medical conditions listed and she took acetaminophen when she experienced chest pain. Given the lack of significant ECG findings and unchanged vital signs from baseline it was less likely due to the drug. In the Infections class, one subject reported nasopharyngitis in the OX22 10 mg (FII, Food) group (1/18=5.6%).

7.4.2 Laboratory Findings

In most studies, laboratory data was collected pre-study and end of study except for pregnancy tests that were done at certain interval visits. For the crossover studies, subjects with clinically relevant values were counted in each treatment group by the Sponsor. The incidence rates are **interpreted as "no greater than", and the rates are reported as a worse-case scenario. The** following criteria was used for significant lab values.

Criteria for Clinically Significant Laboratory Values

	Test	High	Low
Chemistry	BUN	≥ 30 mg/dl	---
	Creatinine	≥ 2 mg/dl	---
	Total Bilirubin	≥ 2 mg/dl	---
	Alkaline Phosphatase	≥ 3x ULN	---
	SGOT	≥ 3x ULN	---
	SGPT	≥ 3x ULN	---
	TSH	≥ 5 mE/L	---
Hematology	Hemoglobin Male Female	 ≥ 18.5 g/dl ≥ 16.5 g/dl	 ≤ 11.5 g/dl ≤ 9.5 g/dl
	Hematocrit Male Female	 ≥ 55% ≥ 50%	 ≤ 37% ≤ 32%
	White Blood Cells	≥ 16 x 10^3/mm^3	≤ 2.8 x 10^3/mm^3
	Eosinophils	≥ 10%	---
	Platelet Count	≥ 700 x 10^3/mm^3	≤ 75 x 10^3/mm^3

ULN = Upper Limit of Normal

Pooling of data was not done since different formulations were used during the trials. Reviewer comments: review of the liver function tests, renal function tests and the hematological parameters did not reveal any clinically significant changes. No additional analysis or explorations were performed. There was one female subject in Study OX22-001 (OX22 5mg, OX22 10 mg, Stilnoct) and 4 subjects (3 males, 1 female) in Study OX22-005 (OX22 FII Fasting, OX22 FII Food, Ambien) with TSH values ≥ 5 mE/L. These subjects began with TSH values in the normal range and the maximum TSH achieved was 6 mE/L. Of note, TSH values were collected in healthy volunteers in Studies OX22-001, 004, 005, and 008; TSH was not collected for insomnia patients (Studies OX22-006, and 007) nor the healthy volunteers in Study OX22-002.

Clinically relevant lab values summary.

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}Laboratory Test	Clinically Relevant Range	OX22 5 mg (FI) (N=37) n(%)	OX22 10 mg (FI) (N=50) n(%)	OX22 10 mg (FII, Fasting) (N=120) n(%)	OX22 10 mg (FII, Food) (N=18) n(%)	OX22 10 mg (FCP) (N=79) n(%)	Stilnoct® 10 mg (N=38) n(%)	Ambien® 10 mg (N=91) n(%)
BUN	>=30 mg/dl	0	0	0	0	0	0	0
Creatinine	>=2 mg/dl	0	0	0	0	0	0	0
Total Bilirubin	>=2 mg/dl	0	0	0	0	0	0	0
Alkaline Phosphatase	>= 3x ULN	0	0	0	0	0	0	0
SGOT	>= 3x ULN	0	0	0	0	0	0	0
SGPT	>= 3x ULN	0	0	0	0	0	0	0
TSH (a)	>=5 mE/L	1 (2%)	1 (2%)	4 (3%)	4 (22%)	0	1 (2%)	4 (4%)
Hemoglobin	>= 18.5 mg/dl (male), >= 16.5 mg/dl (female)	0	0	0	0	0	0	0
	<= 11.5 g/dl (male), <= 9.5 g/dl (female)	0	0	0	0	0	0	0
Hematocrit	<= 37% (male), <= 32% (female)	1 (2%)	1 (2%)	0	0	0	1 (2%)	0
	>= 55% (male), >= 50% (female)	0	0	0	0	0	0	0
White Blood Cells	>= 16 x 103/mm 3	0	0	0	0	0	0	0
	<= 2.8 x 103/mm 3	0	0	0	0	0	0	0
Eosinophils	>= 10%	0	0	0	0	0	0	0
Platelet Count	>= 700 x 103/mm 3	0	0	0	0	0	0	0
	<= 75 x 103/mm 3	0	0	0	0	0	0	0

Copied from page 34 of 99, Module 5.3.5.3.2, Integrated Summary Safety

OX22-006 double blind single dose study

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}Laboratory Test	Clinically Relevant Range	OX22 10 mg (FII, Fasting) (N=120) n(%)	Ambien® 10 mg (N=91) n(%)
BUN	>=30 mg/dl	0	0
Creatinine	>=2 mg/dl	0	0
Total Bilirubin	>=2 mg/dl	0	0
Alkaline Phosphatase	>= 3x ULN	0	0
SGOT	>= 3x ULN	0	0
SGPT	>= 3x ULN	0	0
TSH	>=5 mE/L	0	0
Hemoglobin	<= 11.5 g/dl (male), <= 9.5 g/dl (female)	0	0
	>= 18.5 mg/dl (male), >= 16.5 mg/dl (female)	0	0
Hematocrit	>= 55% (male), >= 50% (female)	0	0
	<= 37% (male), <= 32% (female)	0	0
White Blood Cells	<= 2.8 x 10^3/mm ^{3}	0	0
	>= 16 x 10^3/mm	0	0
Eosinophils	>= 10%	0	0
Platelet Count	>= 700 x 10^3/mm ^{3}	0	0
	<= 75 x 10^3/mm ^{3}	0	0

Copied from page 35 of 99, Module 5.3.5.3.2, Integrated Summary Safety

7.4.3 Vital Signs

Vital signs were collected pre-study, at baseline, and at end of study including interval in-hospital visits.

Criteria for Clinically Significant Vital Signs Values

Parameter	Classification	Ranges
Systolic BP	High	≥150mg Hg OR ≥20 mm increase *
	Low	<90mg Hg OR >20 mm decrease *
Diastolic BP	High	≥100mg Hg OR ≥15 mm increase *
	Low	<50mg Hg OR >15 mm decrease *
Heart Rate	High	≥120 bpm OR ≥15 bpm increase *
	Low	<50 bpm OR >15 bpm decrease *

* increases/decreases based on changes from baseline measurement

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Subjects whose initial values for blood pressure or heart rate were above or below the set thresholds for abnormal values were excluded from the analysis by the Sponsor. Results did not reveal study drug related trends in vital signs or any clinically significant changes. No additional explorations were performed.

Vital signs summary

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 5 mg (FI) (N=37)	OX22 10 mg (FI) (N=50)	OX22 10 mg (FII, Fasting) (N=120)	OX22 10 mg (FII, Food) (N=18)	OX22 10 mg (FCP) (N=79)	Stilnoct® 10 mg (N=38)	Ambien® 10 mg (N=91)
Systolic BP	Number of Subjects	37	50	119	18	74	38	90
	Low	2 (5%)	2 (4%)	12 (10%)	0 (0%)	5 (7%)	2 (5%)	10 (11%)
	High	1 (3%)	1 (2%)	10 (8%)	0 (0%)	5 (7%)	1 (3%)	10 (11%)
Diastolic BP	Number of Subjects	37	50	119	17	76	38	90
	Low	6 (16%)	6 (12%)	11 (9%)	2 (12%)	2 (3%)	6 (16%)	11 (12%)
	High	2 (5%)	3 (6%)	21 (18%)	1 (6%)	2 (3%)	2 (5%)	20 (22%)
Heart Rate	Number of Subjects	35	46	106	10	73	36	83
	Low	8 (23%)	7 (15%)	16 (15%)	2 (20%)	4 (5%)	8 (22%)	16 (19%)
	High	4 (11%)	5 (11%)	17 (16%)	0 (0%)	8 (11%)	4 (11%)	16 (19%)

Copied from page 36 of 99, Module 5.3.5.3.2, Integrated Summary Safety

OX22-006 double blind single dose study

{tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}		OX22 10 mg (FII, Fasting) (N=72)	Ambien® 10 mg (N=73)
Systolic BP	Number of Subjects	71	72
	Low	10 (14%)	10 (14%)
	High	10 (14%)	10 (14%)
Diastolic BP	Number of Subjects	72	73
	Low	9 (12%)	9 (12%)
	High	19 (26%)	19 (26%)
Heart Rate	Number of Subjects	72	73
	Low	14 (19%)	14 (19%)
	High	16 (22%)	16 (22%)

Copied from page 36 of 99, Module 5.3.5.3.2, Integrated Summary Safety

7.4.4 Electrocardiograms (ECGs)

"ECGs were collected pre-study, and at end of study. QTc calculations were performed using Bazett's formula for all studies except for OX22-007, for which Hodges formula was utilized. A clinically relevant ECG value was defined as QTc values > 500 msec and QTc changes of 30-60 msec and >60 msec. Mean QTc values at end of study ranged from 405 msec to 430 msec. The changes from baseline were small for studies that included the OX22 FCP treatment, with a **mean change of 0.4 msec."**

In study OX22-006, two subjects (332-001 and 701-015) on Formulation II had end of study EKG QTc prolongations from baseline > 60 msec; the QTc values in these two subjects, 401 msec and 430 were not significantly elevated. Ten subjects in the program had changes in the QTc of 30-60 msec. There was no evidence of a drug-related effect on QTc prolongation from OX22.

7.4.5 Special Safety Studies

Additional safety studies to assess the effect of drug withdrawal and/or abuse potential, rebound, or dose-relationship of adverse events were not determined by the Sponsor since they were relying on the RLD Ambien label for such information.

7.4.6 Immunogenicity

There was no immunogenecity data provided to assess the impact of immunogenecity on safety, efficacy, clinical pharmacokinetics or pharmacology.

7.5 Additional Safety Explorations

7.5.1 Human Carcinogenicity, mutagenesis, and impairment of fertility

The following text is taken directly from the currently approved label for Ambien.

"Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10 mg human dose on a mg/kg or mg/m2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10 mg human dose on a mg/kg or mg/m2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were

comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

Impairment of fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m2. No effects on any other fertility parameters were noted."

7.5.2 Human Reproduction and Pregnancy Data

One 45 year old subject in study OX22-006 while on the Ambien arm of the study was exposed to single dose of drug, with a negative urine pregnancy test and serum hCG results pending at the time of enrollment. She was withdrawn from the study after results were obtained, however she had spontaneous abortion approximately 2 weeks later. Subsequent serum hCG results were negative. This was reported as SAE.

The following is from the approved label for Ambien®:

Pregnancy
"*Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. Ambien should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Oral studies of zolpidem in pregnant rats and rabbits showed adverse effects on the development of offspring only at doses greater than the maximum recommended human dose (MRHD of 10 mg/day). These doses were also maternally toxic in animals. A teratogenic effect was not observed in these studies. Administration to pregnant rats during the period of organogenesis produced dose-related maternal toxicity and decreases in fetal skull ossification at doses 25 to 125 times the MRHD. The no-effect dose for embryo-fetal toxicity was between 4 and 5 times the MRHD. Treatment of pregnant rabbits during organogenesis resulted in maternal toxicity at all doses studied and increased post-implantation embryo-fetal loss and under-ossification of fetal sternebrae at the highest dose (over 35 times the MRHD). The no-effect level for embryofetal toxicity was between 9 and 10 times the MRHD. Administration to rats during the latter part of pregnancy and throughout lactation produced maternal toxicity and decreased pup growth and survival at doses approximately 25 to 125 times the MRHD. The no-effect dose for offspring toxicity was between 4 and 5 times the MRHD.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have

not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and delivery
Ambien has no established use in labor and delivery.

Nursing mothers
Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal subjects (2.6 ± 0.3 hr). Between 0.004% and 0.019% of the total administered dose is excreted into milk. The effect of zolpidem on the nursing infant is not known. Caution should be exercised when Ambien is administered to a nursing mother.

7.5.3 Pediatrics and Effect on Growth

The following is from the approved label for Ambien®:

"Safety and effectiveness of zolpidem have not been established in pediatric patients.
In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics) were treated with an oral solution of zolpidem (n=136), or placebo (n=65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) *[see Warnings and Precautions(5.6)]*. Ten patients on zolpidem (7.4%) discontinued treatment **due to an adverse reaction."**

Data on growth parameters is not available.

7.5.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Ambien is a class IV controlled substance.
There were two reports of administration above the recommended dosage regimen of OX22 in the clinical program in study OX22-007.

- Patient 015 documented that, on 2 different nights, her spouse informed her that she got up in the middle of the night and took another sublingual Zolpidem tartrate sublingual tablet. These occurrences were recorded as an AE - mild parasomnia, which was considered related to study medication and resolved without treatment.
- Patient 046 purposefully took 2 doses of sublingual Zolpidem tartrate sublingual tablets 8 hours apart (at 14:00 and 22:00) for 3 consecutive days. This patient did not report any AEs during this study.

7.6 Additional Submissions

There were no relevant additional submissions.

8 Postmarketing Risk Management Plan

There was no postmarketing risk management plan submitted for this product.

9 Appendices

9.1 Literature Review/References

General
The Sponsor provided an adequate selection of references from the sleep literature for this review using basic search terms "Zolpidem, Ambien®, Stilnoct®, Stilnox®." The references were provided as summary in addition to full text hotlinks to .pdf files in different sections of the aplication. The literature searches were performed using Medline and Toxnet databases until November 2, 2007 with an update in February 2008. In addition safety data mining in postmarketing data was performed using the AERS system. The Sponsor submitted data on the 20 most frequent adverse reactions occurring in male and female patients of all ages including pediatric, adult, and elderly individuals.

The most common TEAE reported by outpatients with insomnia was headache, reported by 43% of subjects in the zolpidem 10 mg group (Fry et al., 2000). In a post-marketing surveillance study that investigated the safety of zolpidem [administered as 5 mg, 10 mg, or 20 mg doses (or greater)] in 16,944 cases of patients with sleep disturbances, the most common AEs were nausea, dizziness, malaise, nightmares, agitation, and headache. There was no difference in the frequency of AE reporting between dose groups (Hajak and Bandelow, 1998).

Neurobehavioral effects
Persisting and long-term effects with zolpidem use has been reported in the literature, including memory impairment. Impairment of the ability to drive after taking zolpidem tartrate oral tablets was not seen when it was taken the night before driving (e.g., 9 to 11 hours prior to driving), in a number of published studies; however, driving impairment has been reported when zolpidem was taken closer to driving (e.g., 5.5 hours).

Hallucinations and sensory distortions (auditory and tactile) appear to have the most clinical significance just due to the sheer number of reports of individuals in various age groups (13-94 years) who experienced this AE from doses 20mg up to 300mg/day. In a few cases there were

other concomitant medications that may have contributed to this effect. A 34 year old female who was treated for chronic insomnia with 5 mg took an additional 5mg when she was not getting much relief on the current dose. At this therapeutic dose, she experienced a variety of sensory distortions which began approximately 20 minutes after dosing (Pies, 1995).

Cardiac effects
In the OX22 program, although two subjects receiving Formulation II had an end of study QTc prolongation form baseline > 60 msec, there was no evidence of a drug-related effect on QTc prolongation from zolpidem tartrate sublingual tablets. From the published literature, 1 subject taking zolpidem tartrate oral tablets with a history of prosthetic mitral valve and congestive heart failure was reported to have an increased QTc and developed torsades de pointes (TdP), four days following initiation of amiodarone treatment. It is not clear whether the TdP was a result of the amiodarone treatment.

There is a single occurrence of QTc prolongation detailed in a case report. A 67 year-old woman who had a history of prosthetic mitral valve and congestive heart failure (NYHA II) and who was taking captopril, furosemide, warfarin, and zolpidem was admitted to the emergency room complaining of palpitations. Upon admission, her ECG showed sinus rhythm with left bundle branch block (LBBB), premature ventricular complexes, and a QTc interval of 440 msec. Transthoracic echocardiography revealed global wall motion abnormalities of the left ventricle with an estimated ejection fraction of 45%. ECG Holter monitoring showed mulifocal premature ventricular complexes, couplets, and episodes of bigeminy and trigeminy. Intravenous amiodarone was started. On the fourth day, she developed torsades de pointes (TdP) ventricular tachycardia which degenerated to ventricular fibrillation, and required defibrillation to restore sinus rhythm. A marked QTc interval prolongation (565 msec) was recorded before the episode. No evidence of ischemia was present; laboratory tests were normal. Zolpidem and amiodarone were discontinued. Over the following days, the QTc interval gradually decreased to its initial value (Letsas et al., 2006).

Accidental exposures and Deaths
A retrospective review of accidental and purposeful pediatric exposures to zolpidem found that hallucinations were reported in 1 in 7 cases of unintentional exposure and 1 in 5 cases of intentional exposure (Kurta et al., 1997). This is reflected also in the current label under Pediatric use.

The deaths reported following oral zolpidem administration had other confounding factors. In a retrospective analysis of 344 cases of acute intentional overdose with zolpidem reported to a poison control center, fatalities were reported for 6% of cases, but could not be directly linked to zolpidem (Garnier et al., 1994). Zolpidem was involved in 8 cases investigated by the Maryland Chief Medical Examiner. Three deaths were not caused by drugs; of the 5 deaths due to drug intoxication, zolpidem was present, but the deaths were caused by the ingestion of other drugs in 3 cases, and in the other 2 cases, zolpidem was elevated and was considered a contributing but not exclusive cause of death (Levine et al., 1999).

9.2 Labeling Review

The Sponsor chose Ambien® as the RLD and its approved April 23, 2008 version of the drug label. Changes were made to the following sections of the label:

Highlights of prescribing information
1 INDICATIONS AND USAGE
2.4 Administration
6.1 Incidence in clinical trials of zolpidem tartrate
8.4 Pediatric use
10.1 Signs and symptoms
14.1 Chronic insomnia
14.3 Studies Pertinent To Safety Concerns For Sedative/Hypnotic Drugs
17.4 Medication guide

- Pharmacodynamic results should be excluded from the indications and clinical trials section for reasons stated in the efficacy section.
- Statement indicating earlier onset of action in relation to meals should be excluded since the earlier statement from the Ambien label reflects the same.
- The Adverse Event section will likely need to be reduced to represent the RLD label since it represents all the observed events. I recommend including in addition only the oral finding in the label seen in study OX22-007.
- Deletion of study findings from OX22-007 describing overdose information as the RLD label is more inclusive.
- Delete clinical studies in section 14.1 except for study OX22-007.

9.3 Advisory Committee Meeting

The Division did not convene an advisory committee meeting to discuss the current study.

9.4 Comments to Applicant

Changes were made to the following sections of the label:

Highlights of prescribing information
1 INDICATIONS AND USAGE
2.4 Administration
6.1 Incidence in clinical trials of zolpidem tartrate
8.4 Pediatric use
10.1 Signs and symptoms
14.1 Chronic insomnia
14.3 Studies Pertinent To Safety Concerns For Sedative/Hypnotic Drugs
17.4 Medication guide

9.5 Treatment Emergent Adverse Events in OX22 Clinical Program

System Organ Class	Preferred Term	OX22 5 mg (FI) (N=37) n(%)	OX22 10 mg (FI) (N=50) n(%)	OX22 10 mg (FII, Fasting) (N=120) n(%)	OX22 10 mg (FII, Food) (N=18) n(%)	OX22 10 mg (FCP) (N=79) n(%)	Stilnoct® 10 mg (N=38) n(%)	Ambien® 10 mg (N=91) n(%)
CARDIAC DISORDERS	PALPITATIONS	0	0	0	0	1 (1.3)	0	0
	SINUS BRADYCARDIA	0	0	1 (0.8)	0	0	0	0
EAR AND LABYRINTH DISORDERS	EAR PAIN	0	0	0	0	1 (1.3)	0	0
	VERTIGO	0	0	0	0	1 (1.3)	0	0
EYE DISORDERS	DIPLOPIA	0	3 (6.0)	1 (0.8)	0	0	0	1 (1.1)
	EYE PAIN	0	0	1 (0.8)	0	1 (1.3)	0	0
	VISION BLURRED	0	0	1 (0.8)	0	2 (2.5)	0	0
GASTRO-INTESTINAL DISORDERS	ABDOMINAL PAIN	0	0	0	0	1 (1.3)	0	0
	ABDOMINAL PAIN UPPER	0	1 (2.0)	0	0	1 (1.3)	0	0
	APHTHOUS STOMATITIS	0	0	0	0	1 (1.3)	0	0
	CONSTIPATION	0	0	0	0	1 (1.3)	0	0
	DIARRHOEA	0	0	0	0	1 (1.3)	0	0
	DRY MOUTH	0	0	1 (0.8)	0	0	0	0
	DYSGEUSIA	0	0	2 (1.7)	0	0	0	2 (2.2)
	GASTRITIS	0	0	0	0	1 (1.3)	0	0
	GASTROOESOPHAGEAL REFLUX DISEASE	0	0	0	0	2 (2.5)	0	0
	GLOSSITIS	0	0	0	0	1 (1.3)	0	0
	NAUSEA	3 (8.1)	1 (2.0)	4 (3.3)	1 (5.6)	5 (6.3)	0	5 (5.5)
	PARAESTHESIA ORAL	0	0	0	0	1 (1.3)	0	0
	STOMACH DISCOMFORT	0	0	0	0	1 (1.3)	0	0
	TOOTHACHE	0	0	0	0	2 (2.5)	0	0
	VOMITING	1 (2.7)	1 (2.0)	0	0	2 (2.5)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	0	0	0	0	0	0	1 (1.1)
	CHEST PAIN	0	0	0	1 (5.6)	1 (1.3)	0	0
	FATIGUE	2 (5.4)	2 (4.0)	1 (0.8)	0	6 (7.6)	0	0
	HANGOVER	0	0	1 (0.8)	0	0	0	0
	MALAISE	0	1 (2.0)	0	0	0	0	0
	OEDEMA PERIPHERAL	0	0	0	0	1 (1.3)	0	0
	PAIN	0	0	0	0	1 (1.3)	0	0
	PYREXIA	0	0	0	0	1 (1.3)	0	0
INFECTIONS AND INFESTATIONS	GASTROENTERITIS VIRAL	0	0	0	0	1 (1.3)	0	0
	HERPES SIMPLEX	0	0	1 (0.8)	0	0	0	0
	INFLUENZA	0	0	1 (0.8)	0	0	0	1 (1.1)
	NASOPHARYNGITIS	1 (2.7)	0	1 (0.8)	1 (5.6)	1 (1.3)	0	0
	PHARYNGITIS	0	0	0	0	1 (1.3)	0	0
	RHINITIS	0	1 (2.0)	0	0	0	0	0
	UPPER RESPIRATORY TRACT INFECTION	0	0	0	0	2 (2.5)	0	0
PROCEDURAL COMPLICATIONS	PROCEDURAL PAIN	0	0	0	0	1 (1.3)	0	0
INVESTIGATIONS	BLOOD THYROID STIMULATING HORMONE INCREASED	0	1 (2.0)	0	1 (5.6)	0	0	1 (1.1)
METABOLISM AND NUTRITION DISORDERS	IRON DEFICIENCY ANAEMIA	0	0	1 (0.8)	0	0	0	0

System Organ Class	Preferred Term	OX22 5 mg (FI) (N=37) n(%)	OX22 10 mg (FI) (N=50) n(%)	OX22 10 mg (FII, Fasting) (N=120) n(%)	OX22 10 mg (FII, Food) (N=18) n(%)	OX22 10 mg (FCP) (N=79) n(%)	Stilnoct® 10 mg (N=38) n(%)	Ambien® 10 mg (N=91) n(%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	0	0	0	0	1 (1.3)	0	0
	BONE PAIN	0	0	0	0	1 (1.3)	0	0
	HYPOTONIA	0	0	1 (0.8)	0	0	0	0
	INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (1.3)	0	0
	SENSATION OF HEAVINESS	0	0	2 (1.7)	0	0	0	0
	TENDONITIS	0	0	0	0	1 (1.3)	0	0
NERVOUS SYSTEM DISORDERS	AMNESIA	0	0	1 (0.8)	0	0	0	0
	BALANCE DISORDER	0	0	0	0	3 (3.8)	0	0
	COORDINATION ABNORMAL	0	0	0	0	1 (1.3)	0	0
	DIZZINESS	1 (2.7)	3 (6.0)	6 (5.0)	1 (5.6)	10 (12.7)	2 (5.3)	2 (2.2)
	HEADACHE	2 (5.4)	6 (12.0)	4 (3.3)	0	5 (6.3)	0	2 (2.2)
	HYPERSOMNIA	0	0	0	0	0	0	1 (1.1)
	HYPOAESTHESIA	0	0	0	1 (5.6)	1 (1.3)	0	0
	MIGRAINE	0	0	0	0	0	0	1 (1.1)
	PARAESTHESIA	0	0	0	0	3 (3.8)	0	0
	SEDATION	0	0	0	0	1 (1.3)	0	0
	SOMNOLENCE	3 (8.1)	1 (2.0)	3 (2.5)	0	8 (10.1)	1 (2.6)	2 (2.2)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	ABORTION SPONTANEOUS	0	0	0	0	0	0	1 (1.1)
	AGITATION	0	0	0	0	1 (1.3)	0	0
	DEPRESSED MOOD	1 (2.7)	0	0	0	1 (1.3)	0	0
	DISORIENTATION	0	0	0	0	1 (1.3)	0	0
PSYCHIATRIC DISORDERS	HALLUCINATION	0	0	0	0	1 (1.3)	0	0
	NERVOUSNESS	0	0	0	0	1 (1.3)	0	0
	NIGHTMARE	0	0	1 (0.8)	0	0	0	0
	PARASOMNIA	0	0	0	0	2 (2.5)	0	0
	SLEEP DISORDER	1 (2.7)	0	0	0	0	0	0
RENAL AND URINARY DISORDERS	DYSURIA	0	0	0	0	1 (1.3)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	0	0	0	0	1 (1.3)	0	0
	BRONCHITIS ACUTE	0	0	0	0	0	0	1 (1.1)
	EPISTAXIS	0	0	0	0	1 (1.3)	0	0
	HICCUPS	0	2 (4.0)	0	0	0	0	0
	RESPIRATORY DISORDER	0	0	0	0	0	0	1 (1.1)
	RHINITIS ALLERGIC	0	0	0	0	0	0	1 (1.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ACNE	0	0	0	0	1 (1.3)	1 (2.6)	0
	ERYTHEMA	1 (2.7)	0	1 (0.8)	0	1 (1.3)	0	0
	INGROWING NAIL	0	0	0	0	1 (1.3)	0	0
	PRURITUS GENERALISED	1 (2.7)	0	0	0	0	0	0
	RASH	1 (2.7)	0	0	0	0	0	0
	RASH MACULAR	0	1 (2.0)	0	0	0	0	0
	RASH PAPULAR	0	0	0	0	0	1 (2.6)	0
VASCULAR DISORDERS	HOT FLUSH	0	1 (2.0)	0	0	0	0	0

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/s/

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3/10/2009 06:20:30 PM
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