CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022328Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#	**22328/S0043**
Submission Date:	8/31/2011
End of Review Meeting Date:	9/14/2011
Generic Name:	Zolpidem
Formulation:	Sublingual Tablet
Sponsor:	Tanscept Pharmaceuticals
Reviewer:	Jagan Mohan Parepally, Ph.D.
Submission Type:	Type A, End of Review Meeting Package

BACKGROUND

The Agency issued a second complete response (CR) letter on July 14, 2011 to the sponsor. In response to the CR letter the sponsor requested the End of Review meeting.

The purpose of this meeting is to discuss sponsor's proposed response to the concerns raised in the CR letter. Following are some of the concerns listed in the Agency's CR letter issued to the sponsor.

- Potential for inadvertent misuse, (double dosing and inability to properly time dosing vs. morning activities such as driving).
- Concern that morning plasma levels may be elevated, resulting in increased risk of morning sedation and consequent potential for driving impairment.
- Possible demographic PK differences.
- Outliers in the driving study.

The sponsor's responses to some of the FDA's concerns

1. 4-Hour Plasma Levels in Subjects at the High-End of Zolpidem Exposure from Intermezzo

According to the sponsor's t-test analysis there was no evidence of any correlation between concentration levels and impairment as measured by DSST.

Study ZI-05-009
t-test: in male subjects the effect of Intermezzo on DSST performance was not statistically different from placebo at any of the time points. In female subjects the effect of Intermezzo on DSST performance was statistically significantly different from placebo for up to 180 minutes.

Reviewer's Comment: The Agency does not believe that DSST is the validated measure for assessment of next day residual effects including driving performance though DSST did not show any correlation with the zolpidem concentration.

2. Effect of Race and Body Weight on Zolpidem Pharmacokinetics

The sponsor concludes that on the basis of their data and information in the literature racial differences and body weight do not significantly influence the pharmacokinetics of zolpidem. The sponsor also cites example of approval of zolpidem in Japan where studies related to ethnic differences were conducted for approval.

Reviewer's Comment: Clinical pharmacology reviewer's previous analysis of the data analysis to see correlation between body weight and PK did not show any correlation. The effect of race and body weight will be considered in further analysis including several studies conducted for zolpidem.

The sponsor is proposing following changes in the recommended dosage and administration of Intermezzo:

- Reduce the dose in women to 1.75 mg which is the same as the currently proposed dose in the elderly.
- (b) (4) [redacted]

Awakening in the middle of the night (MOTN) followed by difficulty returning to sleep is a common manifestation of insomnia. The only hypnotics currently approved to treat MOTN awakening are labeled to be taken at bedtime and require 7–8 hours of available time to sleep to assure safe use.

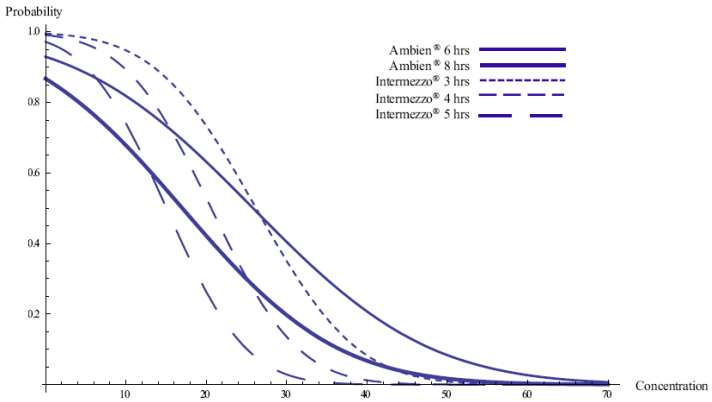
The sponsor argues that the dose of zolpidem in Intermezzo is between 28% and 33% of currently approved zolpidem products, and dosed only in the middle of the night when actually needed, will substantially reduce overall hypnotic exposure vs. bedtime prophylactic dosing of 7-8 hour hypnotics and specifically packaged for MOTN use to mitigate accidental double dosing.

According to the sponsor (further analysis of the data):

- In men, the post dose probability of ~ 40 ng/ml plasma levels from 3.5 mg Intermezzo is similar at 3 hours, and less than at 4 and 5 hours, vs. Ambien 10 mg at 8 hours.
- In women, the post dose probability of ~ 40 ng/ml plasma levels from 3.5 mg Intermezzo is similar at 5 hours, but greater than at 3 and 4 hours, vs. Ambien 10 mg at 8 hours.
- At a dose of 1.75 mg in women, the post dose probabilities of ~ 40ng/ml plasma levels at 3, 4 and 5 hours are all less than Ambien 10 mg at 8 hours post dose.
- No meaningful PK differences were found due to body weight differences, or in demographic groups other than women.
- Driving impairment at 4 hours was found to be not different than placebo as per the statistical analysis. The range of Intermezzo SDLP change from placebo is

similar to the results in driving studies comparing placebo to placebo and placebo to no treatment.

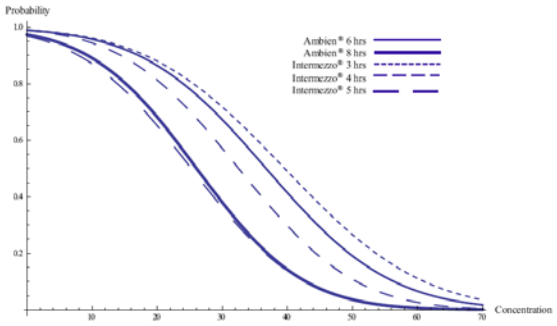
Males: Predictive Probability of exceeding a concentration (ng/ml) with a 3.5 mg dose (untransformed, all studies).



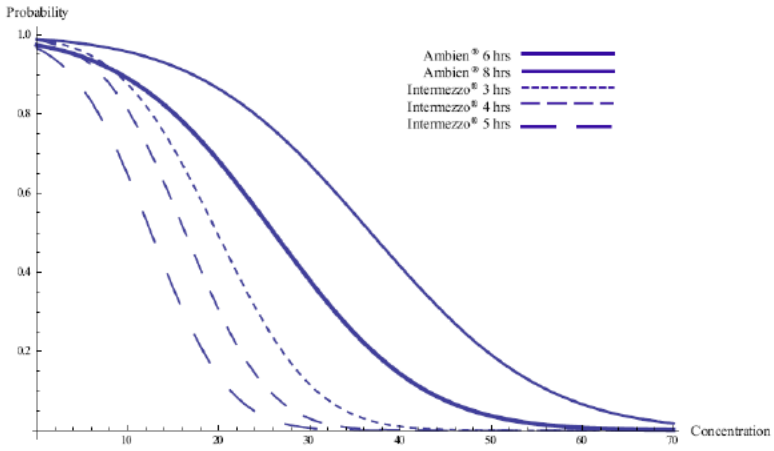
Reviewer's Comment:

Predictive probability curve for Intermezzo at 3 hrs post dose is higher for most part when compared to Ambien at 8 hrs. Therefore, inadvertent dosing with less than 3 hrs of bedtime may lead to higher (>40 ng/mL) blood levels in the morning.

Females: Predictive Probability of exceeding a concentration (ng/ml) with a 3.5 mg dose (untransformed, all studies)



Females: Predictive Probability of exceeding a concentration (ng/ml) with a 1.75 mg dose (untransformed, all studies)



According to the sponsor, covariate analysis of the 3, 4, and 5-hour Intermezzo 3.5 mg plasma levels in men and women did not indicate that age, body weight or race (whites and African-American blacks) influenced the pharmacokinetics of Intermezzo in these subjects.

Based on the above analysis the sponsor proposed following changes to the labeling:

Current language	Proposed language
DOSAGE AND ADMINISTRATION (b) (4)	**DOSAGE AND ADMINISTRATION** (b) (4)
(b) (4)	(b) (4)

Proposed labeling changes related to time before driving are mentioned below:

5.1 [redacted]

[redacted]

Question

Transcept has proposed that reducing the recommended dose for women to 1.75 mg, and [redacted] for all patients addresses the Agency's remaining concerns about risks of next-day impairment. Does the Agency agree that the proposed dose and timing recommendations, which are supported by existing data, adequately address the safety concerns that accounted for the Agency's previous decision to withhold approval of our 505(b)2 NDA for Intermezzo?

Division's Response: We generally agree with your proposal, and believe that if your Complete Response is adequately concise in summarizing morning zolpidem levels and evidence that the levels are safe given this labeling, we may be able to consider the Complete Response a Class 1 resubmission (as described in Guidance for Industry: Classifying Resubmissions in Response to Action Letters, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079303.pdf).

ADDITIONAL COMMENT

In the response to CR letter resubmission, please provide 1) justification for the proposed dose in men and women, and 2) a summary of plasma concentration at 3, 4 and 5 hours post 1.75 and 3.5 mg Intermezzo dose for men and women.

RECOMMENDATION

Clinical Pharmacology additional comment was conveyed at the face-to-face meeting. The sponsor agreed to provide the information requested.

_____ _____

Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

_____ _____

Angela Men, M.D., Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 NDA# 22328
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Mohan Parepally

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/s/

JAGAN MOHAN R PAREPALLY
11/22/2011

YUXIN MEN
11/23/2011

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Zolpidem Tartrate
NDA:	22-328
SUBMISSION DATE	9/23/2011
SUBMISSION TYPE	Re-submission in response to CR letter
PRODUCT (Brand Name):	Intermezzo®
DOSAGE FORM:	Sublingual Tablet
DOSAGE STRENGTHS:	1.75 and 3.5 mg
INDICATION:	As-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN)
NDA TYPE:	505 (b)(2)
SPONSOR:	Transcept Pharma Inc.
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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I. EXECUTIVE SUMMARY

Intermezzo® is a sublingual tablet formulation of zolpidem tartrate. Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class for the short term treatment of insomnia characterized by difficulties with sleep initiation. Oral tablets of zolpidem tartrate are currently marketed under trade name of Ambien®. The current 505(b)(2) NDA seeks approval of Intermezzo® for the treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN). The sponsor proposed 1.75 mg in women and 3.5 mg for men (b) (4)

A Complete Response (CR) letter was issued to the original NDA on October 28, 2009. The Division agreed that the proposed indication is adequately supported, but was concerned about the safety risk from residual morning levels of drug, particularly if there was inadvertent re-dosing of Intermezzo in a single night, or inadvertent dosing with less than 4 hours of bedtime remaining. The sponsor submitted a response to the CR letter on January 14, 2011, which included a driving study to address the safety risk associated with the residual effects in the next morning. The Division issued a second CR on 7/14/2011 to the January submission. The Division indicated that the sponsor should specifically to:

1. Characterize more thoroughly the distribution of blood levels that can occur the morning after Intermezzo dosing.
2. Pursue strategies to decrease morning zolpidem levels from Intermezzo, particularly levels at the high end of the distribution (e.g. through modification of dose, time, patient selection, etc.).
3. Depending on the residual zolpidem level that might result after mitigation strategies were implemented, demonstrate that the levels did not present an unacceptable risk of next-day impairment.

The Division also suggested decreasing morning zolpidem levels through modification of dose, time, patient selection, etc. since women had 40% to 70% higher zolpidem concentrations when compared to men at the same dose.

In this submission, the sponsor modified the dose of Intermezzo in women and submitted the pharmacokinetic (PK) data concerning **next morning residual blood levels**, including the demographic factors' impact on the PK of zolpidem and the distribution of blood levels at different time after administration to support the approval of Intermezzo at the proposed dose in women (1.75 mg) and men (3.5 mg).

A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the additional clinical Pharmacology summary for NDA 22-328 supporting the revised dosing, 1.75 mg in women and 3.5 mg for men 4-hr before awakening. The submission is acceptable from a

Clinical Pharmacology perspective provided mutual agreement reached regarding the labeling recommendations in the package insert.

B. Phase IV Commitments

None.

C. Summary of Clinical Pharmacology Data Supporting Revised Dosing

To support the proposed dosing recommendation of Intermezzo® 1.75 mg in women and 3.5 mg in men 4-hour before awakening, the sponsor provided the following summary of pharmacokinetic data.

Pharmacokinetic data concerning next morning residual blood levels

Study ZI-05-009 is a double-blind, placebo controlled study which investigated the PK and pharmacodynamics (PD) of Intermezzo doses of 1.0, 1.75 and 3.5 mg in 11 non-elderly women and 13 non-elderly men. The results demonstrated that, at the same dose, Intermezzo plasma levels were approximately 45% higher in women than men. Higher plasma levels in women are mostly attributed to lower apparent sublingual clearance of the drug. The lower clearance in women could not be explained by body weight, since the difference is still evident after normalization for body weight.

The data suggests that when the Intermezzo dose in women is reduced from 3.5 to 1.75 mg, zolpidem exposure from Intermezzo should decrease proportionally by about 50%.

The predictive probability of Intermezzo 1.75 mg producing a plasma level of 40 ng/ml or higher in women at 3, 4, and 5 hours post-dose (0.01) is lower than that of 10 mg zolpidem measured at 6 and 8 hours post-dose (0.412).

In men, the predictive probability of Intermezzo 3.5 mg producing a plasma level of 40 ng/ml or higher at 3, 4, and 5 hours post-dose (<0.09) is similar to or lower than that of 10 mg zolpidem measured at 8 hours post-dose (0.065).

Zolpidem blood levels after 4 hrs following 1.75 mg dose in women and 3.5 mg dose in men were shown to have a 0.1% probability of being above 40 ng/mL in women and 1% in men. Therefore dosing recommendation specifically 'Intermezzo should only be taken if the patient has atleast 4 hrs of bedtime' would be sufficient (b) (4)

Effect of other demographic factors on Intermezzo plasma levels

Zolpidem plasma concentrations from non-elderly women and nonelderly men pooled from 3, 4, and 5 hours were analyzed with body weight and race (African-Americans and non-African-Americans). The results showed that the covariates did not significantly

influence the zolpidem plasma levels. However, greater variability was seen in African American population when compared to Caucasians.

_____ _____

Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

_____ _____

Angela Men, M.D., Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 NDA 22-328
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Parepally

II. QUESTION BASED REVIEW

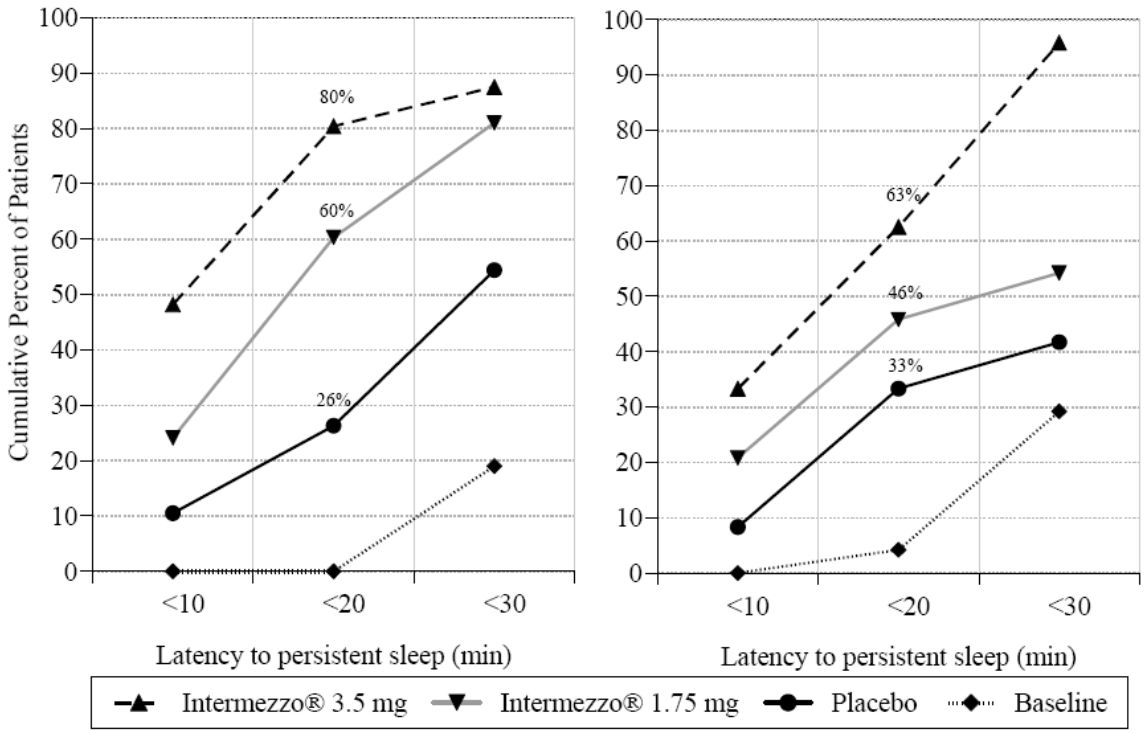
A. General Clinical Pharmacology

Refer to the original Clinical Pharmacology Review for Intermezzo® in DARRTS dated 7/23/2009.

What is the clinical efficacy data used to support dosing in women and men?

The efficacy data to support Intermezzo 1.75 mg and 3.5 mg dose in women and men, respectively, are derived from the sleep laboratory study (ZI-06-010). This study was a double-blind, placebo-controlled clinical crossover study which evaluated the safety and efficacy of 1.75 mg and 3.5 mg doses of Intermezzo in adults (N=82) with a history of middle-of-the-night awakening. Following figure illustrates dose-response (efficacy) data in women and men.

Cumulative % of Patients Asleep (After MOTN Awakening) at Sequential 10-minute Intervals by polysomnography (PSG) (Study ZI-06-010, left: women; right: men)



Sleep latency, the primary endpoint measured by latency of persistent sleep (LPS), was <20 min in 60% of women on 1.75 mg Intermezzo group when compared to 63% of men dosed with 3.5 mg Intermezzo, suggests that comparable dose-response (efficacy) in women and men. This result supports the proposed dose of 1.75 mg and 3.5 mg in women and men respectively.

B. Intrinsic Factors

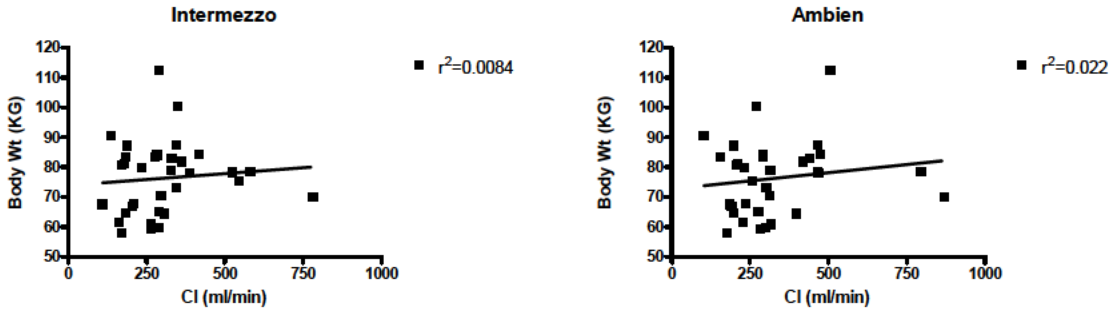
The effects of various intrinsic factors (e.g., hepatic, renal) were provided in the original NDA. Please see Clinical Pharmacology reviews for Ambien® (zolpidem tartrate) tablets NDA 19-908 and the original Clinical Pharmacology Review Intermezzo® in DARRTS dated 7/23/2009.

Body Weight:

Analysis of zolpidem plasma concentration by body-weight indicates that there is no correlation between body-weight and zolpidem clearance when subjects were fix-dosed with Intermezzo or Ambien®.

Following figure represents analysis of PK profile of zolpidem by body-weight from study ZI15, a pivotal bioequivalence study comparing PK profiles of Intermezzo with reference Ambien®.

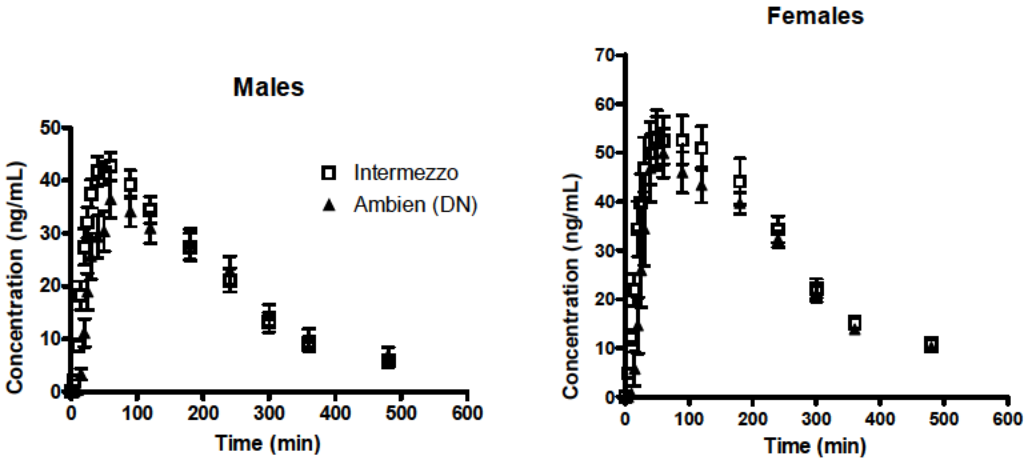
Zolpidem Clearance vs Body Wt.



Gender:

Women on an average had 40% to 70% higher plasma concentration when compared to men at the same dose. Following figure represents analysis of PK profile of zolpidem not corrected for body-weight from study ZI15, a pivotal bioequivalence study comparing PK profiles of Intermezzo (3.5 mg) with reference Ambien® (10 mg). PK profile for Ambien was dose normalized (DN) for comparison.

Zolpidem PK profile by Gender (ZI15)



The PK data from the Study ZI-05-009 in men and women after administration of 1.0, 1.75 mg and 3.5 mg Intermezzo® sublingual tablet is provided as supporting evidence for dosing recommendation in men and women. The mean plasma levels (Cmax, C3, C4 and C5) and AUC of zolpidem from 1.75 mg and 3.5 mg sublingual zolpidem in women and men were comparable to the support the proposed dose.

Study ZI-05-009, a double-blind, placebo controlled study, investigated the PK and PD of Intermezzo doses of 1.0, 1.75 and 3.5 mg in 11 non-elderly women and 13 non-elderly men. The results from the study demonstrated that, at the same dose, zolpidem plasma levels were approximately 45% higher in women than men. Higher plasma levels in women are mostly attributed to lower apparent clearance of the drug. Table below represents PK parameters obtained from Study ZI-05-009.

Mean (SD) Intermezzo Plasma Pharmacokinetic Parameters after Single Dose Administration of Intermezzo 3.5, 1.75 and 1.0 mg in women and men (Study ZI-05-009)

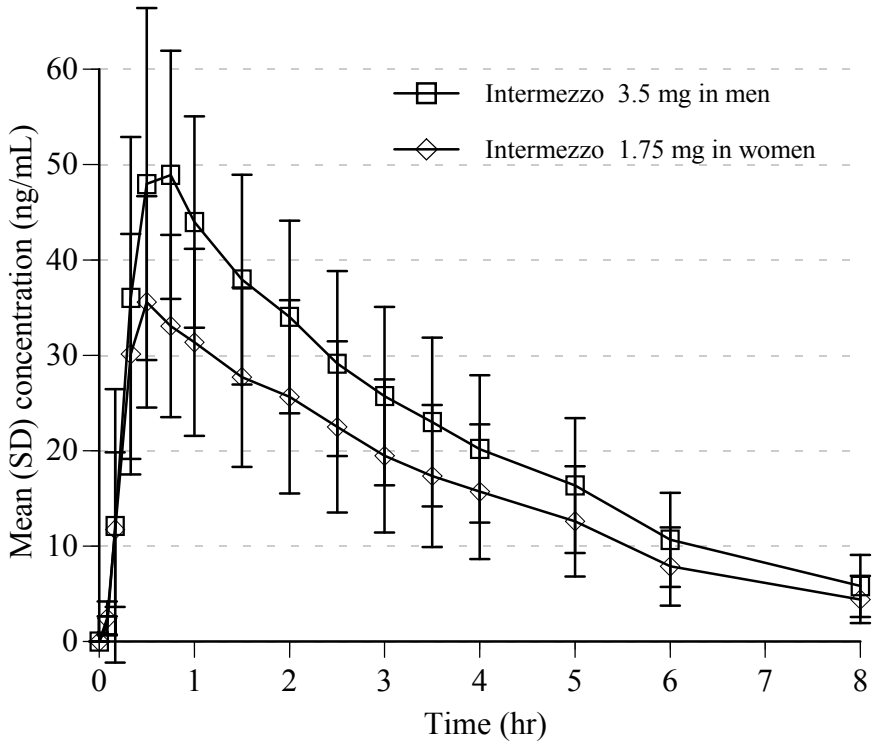
Parameter	Intermezzo 3.5 mg		Intermezzo 1.75 mg		Intermezzo 1.0 mg	
	Women (n=11)	Men (n=13)	Women (n=11)	Men (n=13)	Women (n=11)	Men (n=13)
C_{max} (ng/mL)	77.13 (23.71)	53.15 (14.29)	37.47 (11.10)	27.68 (7.50)	20.12 (6.69)	15.96 (4.77)
t_{max} (h)	0.673 (0.248)	0.596 (0.163)	0.687 (0.377)	0.585 (0.119)	0.588 (0.194)	0.608 (0.169)
AUC_{0-t} (ng.h/mL)	279.97 (95.59)	186.75 (65.24)	142.43 (56.30)	100.18 (32.65)	77.39 (30.09)	56.01 (19.66)

$AUC_{0\text{-inf}}$ (ng h/mL)	295.60 (105.66)	197.69 (72.43)	151.36 (61.54)	104.73 (35.04)	82.30 (32.88)	58.83 (21.20)
t1/2 (h)	2.53 (0.56)	2.38 (0.61)	2.52 (0.64)	2.35 (0.57)	2.58 (0.65)	2.31 (0.61)
C3 (ng/mL)	38.47 (12.80)	25.73 (9.35)	19.46 (8.01)	14.03 (4.55)	10.64 (4.04)	8.13 (2.90)
C4 (ng/mL)	30.32 (11.29)	20.19 (7.73)	15.71 (7.06)	10.82 (3.83)	8.31 (3.26)	6.12 (2.40)
C5 (ng/mL)	26.03 (9.93)	16.36 (7.08)	12.61 (5.78)	8.58 (3.30)	7.01 (3.12)	4.60 (1.91)
app CL(mL/min/kg)	2.66 (0.98)	3.96 (3.70)	2.81 (1.47)	3.85 (4.04)	2.87 (1.24)	3.70 (3.09)

appCL: apparent clearance

The mean plasma levels (Cmax, C3, C4 and C5) and AUC of zolpidem from 1.75 mg and 3.5 mg sublingual zolpidem in women and men were comparable to the support the dose selection, 1.75mg, in women. Following figure represents mean plasma concentrations of zolpidem following administration of 1.75 mg and 3.5 mg dose in women and men respectively.

Mean Plasma Concentration-Time Curve Following Administration of Intermezzo



Race:

Zolpidem plasma concentrations from non-elderly women and nonelderly men pooled from 3, 4, and 5 hours were analyzed with race (African-Americans and non-African-Americans).

Based on the pooled data across the studies, the mean values of zolpidem, C_{max}, C_3, C_4 and C_5, were not significantly different. However, greater variability was seen in African American population when compared to Caucasians.

Mean (%CV) Intermezzo 3.5 mg Cmax and plasma levels at 3, 4, and 5 hours in men

	All Men (n = 96)	**African American Men (n = 35)**	**Caucasian Men (n = 58)**	**Other Men (n = 3)**
Plasma levels (ng/ml)				
C_{max} (ng/mL)	51.07 (32.41)	50.26 (35.10)	52.05 (30.17)	43.74 (51.80)
3 hours	26.20 (37.48)	26.60 (45.76)	26.06 (32.32)	24.52 (31.65)
4 hours	20.62 (40.92)	21.10 (47.70)	20.43 (36.60)	18.61 (39.64)
5 hours	15.05 (51.41)	16.83 (57.25)	14.05 (44.90)	13.64 (48.06)

How does the predictive probability of Intermezzo 1.75 mg producing a plasma level of 40 ng/ml or higher in women at 3, 4, and 5 hours post-dose compare with that of 10 mg zolpidem measured at 6 and 8 hours post-dose?

Data were pooled from all the PK studies conducted for Intermezzo® (women n=81 and men n=96). For the -13, -14, -15, -16, and -17 studies, the1.75 mg plasma levels in women were calculated by dividing the 3.5 mg levels by two.

The predictive probability of Intermezzo producing a plasma level of 40 ng/ml or higher were calculated. Zolpidem blood levels >40 ng/mL was chosen as a rational concentration to be associated with clinically meaningful driving impairment by the Division. The average zolpidem concentration at 3 hrs post dose (3.5 mg) in women was approximately 40 ng/mL. In the driving study ZI18, there was a statistically significant difference in driving performance when driving occurred at 3 hrs post dose (3.5 mg). In addition, the average maximum concentration (Cmax) in women at 1.75 mg dose was 37 ng/mL (at a median Tmax of 0.69 hrs) which corresponds to an effective concentration measured by latency of persistent sleep (LPS, <20 min in 60% of women).
In women at 3, 4, and 5 hours post-dose the predictive probability (0.01) is lower than that of 10 mg zolpidem measured (0.412) at 6 hours and (0.134) at 8 hours post-dose. Following table indicates the predictive probability of attaining 40 ng/mL or higher concentrations with 1.75 or 10 mg zolpidem dose.

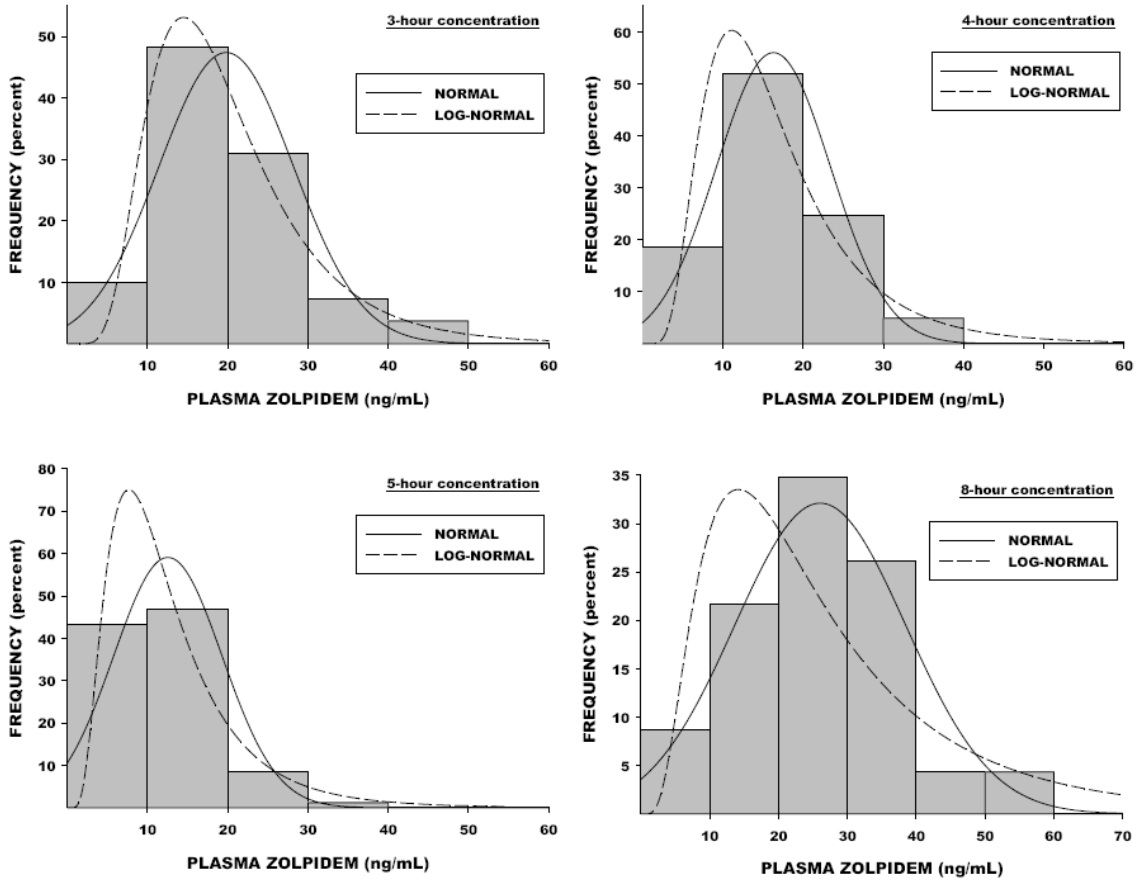
Predictive Probabilities of Exceeding Threshold Plasma Concentration

Values (female subjects)

Plasma concentrations (ng/ml)	Predictive probabilities Intermezzo 1.75 mg (n=81)			Predictive probabilities 10 mg oral zolpidem (n=23)	
	3 hour	4 hour	5 hour	6 hour	8 hour
40	0.010	0.001	0.000	0.412	0.134
50	0.000	0.000	0.000	0.184	0.030
60	0	0	0	0.058	0.004

The figures blow represents actual data distributions in female subjects and corresponding probability density functions based on a normal distribution (solid line) or a log-normal distribution (dashed line). Upper left (C3), upper right (C4), and lower left (C5) graphs are data following 1.75 mg Intermezzo sublingual. Lower right is the 8-hour concentration (C8) in a subset of 23 subjects who took 10 mg of immediate-release zolpidem orally.

Probability Density Functions and Actual Plasma Concentration Distributions in Women



The normal distribution better represents the probability density function when compared to the log-normal distribution. At 4 hours, approximately 2.5% females are predicted to be above 40 ng/ml in the Intermezzo group when compared to approximately 2% above 50 ng/mL at 8 hours in subjects dosed with 10 mg zolpidem.

How does the predictive probability of Intermezzo 3.5 mg producing a plasma level of 40 ng/ml or higher in men at 3, 4, and 5 hours post-dose compare with that of 10 mg zolpidem measured at 6 and 8 hours post-dose?

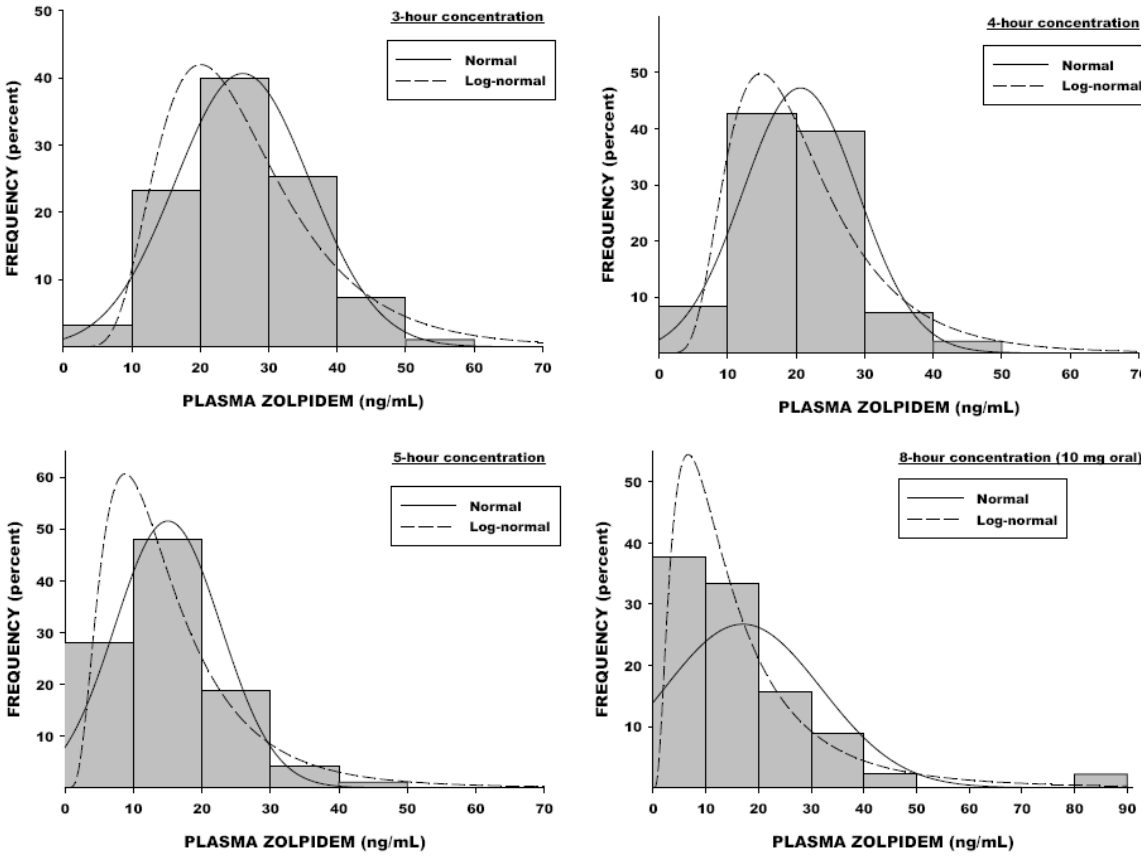
The predictive probability of Intermezzo 3.5 mg producing a plasma level of 40 ng/ml or higher in men at 3, 4, and 5 hours post-dose (0.01) is lower than that of 10 mg zolpidem measured (0.21) at 6 hours and (0.06) at 8 hours post-dose. Following table indicates the predictive probability of attaining 40 ng/mL or higher concentrations with 1.75 or 10 mg zolpidem dose.

Predictive Probabilities of Exceeding Threshold Plasma Concentration Values (male subjects)

Plasma concentrations (ng/ml)	**Predictive probabilities Intermezzo 3.5 mg (n=96)**			**Predictive probabilities 10 mg oral zolpidem (n=45)**	
	3 hour	**4 hour**	**5 hour**	**6 hour**	**8 hour**
40	0.085	0.014	0.001	0.206	0.065
50	0.010	0.001	0.000	0.082	0.016
60	0.001	0.000	0.000	0.025	0.003

Following figure represents actual data distributions in male subjects (expressed as histograms, with categories successively incremented by 10 ng/mL) and corresponding probability density functions based on a normal distribution (solid line) or a log-normal distribution (dashed line). Upper left (C3), upper right (C4), and lower left (C5) graphs are data following 3.5 mg Intermezzo SL. Lower right is the 8-hour concentration (C8) in a subset of 45 subjects who took 10 mg of immediate-release zolpidem orally.

Probability Density Functions and Actual Plasma Concentration Distributions in men



The normal distribution better represents the probability density function when compared to the log-normal distribution in most cases for men. At 4 hours, approximately 1-2% males were predicted to be above 40 ng/ml in both 3.5 mg Intermezzo, and 10 mg zolpidem groups.

In summary, zolpidem blood levels after 4 hrs following 1.75 mg dose in women and 3.5 mg dose in men were shown to have a 0.1% probability of being above 40 ng/mL in women and 1% in men. Therefore dosing recommendation specifically 'Intermezzo should only be taken if the patient has atleast 4 hrs of bedtime' would be sufficient (b) (4)

C. Extrinsic Factors

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

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

D. General Biopharmaceutics

Refer to the original Clinical Pharmacology Review for Intermezzo® in DARRTS dated 7/23/2009.

E. Analytical

Refer to the original Clinical Pharmacology Review for Intermezzo® in DARRTS dated 7/23/2009.

III. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Intermezzo® and finds it acceptable pending the following revision:

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

32 Pages of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAGAN MOHAN R PAREPALLY
11/15/2011

YUXIN MEN
11/15/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

PRODUCT (Generic Name):	Zolpidem Tartrate
NDA:	22-328
SUBMISSION DATES:	1/14/2011, 5/26/2011
PRODUCT (Brand Name):	Intermezzo®
DOSAGE FORM:	Sublingual Tablet
DOSAGE STRENGTHS:	1.75 and 3.5 mg
INDICATION:	As-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN)
NDA TYPE:	505 (b)(2)
SPONSOR:	Transcept Pharma Inc.
SUBMISSION TYPE:	CR Resubmission
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

BACKGROUND

The original NDA for Intermezzo was submitted on September 9th, 2008 and a complete response (CR) letter was issued on October 28th, 2009. (The original Clinical Pharmacology review dated July 23rd, 2009 can be found in DARRTS.) In the CR letter, the Agency indicated that the sponsor failed to demonstrate that Intermezzo can be reliably be used safely in a unique insomnia indication treatment of insomnia characterized by difficulty returning to sleep after middle-of the-night (MOTN) awakening. The average plasma concentration reported at 4 hrs (C_4) after Intermezzo 3.5 mg dosing was approximately similar to the levels noted in the published literature

causing impaired driving. The division also discussed concerns about inadvertent dosing with less than 4 hrs of bedtime remaining and inadvertent re-dosing in a single night. The sponsor conducted a highway driving study to address next-day residual effects in response to the CR letter.

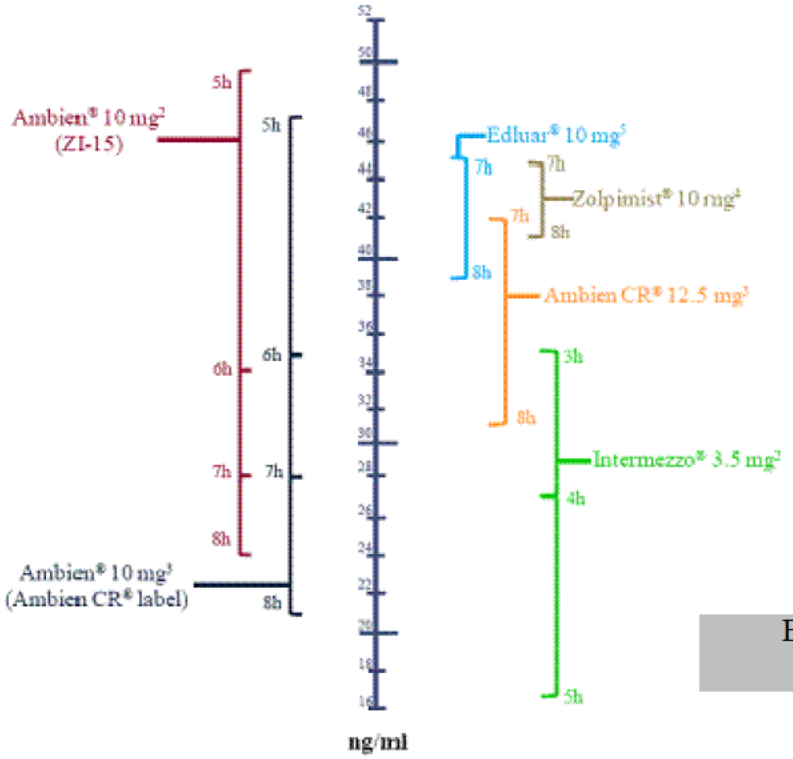
This is a resubmission in response to CR letter including a driving study (ZI-18) submitted on January 14th 2011. Study ZI-18 is single-center, double-blind, randomized, placebo-controlled, four-way crossover study, with 40 adult healthy male and female subjects. Zopiclone (ZOP) was used as positive control in one of the treatment arms. There were 4 (all female subjects) cases of somnolence, 2 each during ZST (Intermezzo) 3h and ZST 4h treatment groups out of which somnolence led to the premature termination of driving tests on 1 occasion in ZST 3hr treatment group. Both the subjects experiencing somnolence in ZST 3hr group were females (subject 0010 and subject 0007). At 3 and 4 hours post dose 10 and 5 subjects were impaired respectively after 3.5 mg dose of Intermezzo at the standard deviation of lateral position (SDLP) threshold of 2.5 cm.

Clinical review division had several queries related to the driving study since the plasma concentrations were not collected in this study to correlate with the next-day residual effects for the subjects failing the driving study. The Agency requested pharmacokinetic (PK) and pharmacodynamic (PD) analysis of all the studies conducted for Intermezzo emphasizing importance of outliers and demographic factors including bodyweight, gender in the PK and PD analysis to explain the next day residual effects (impaired driving) seen in some of the subjects in the driving study. The current submission (submitted May 26th, 2011) includes PK and PD analysis and the analysis of next-day residual effects in all the clinical trials and the driving study after MOTN dosing with Intermezzo.

In support of the plasma concentration of zolpidem resulting from dosing with the Intermezzo, the sponsor provided information related to plasma concentrations of approved zolpidem reported in other NDAs (figure below).

Figure 1: Pharmacokinetic profiles of Ambien®, Ambien® CR, Zolpimist®, Edluar® and Intermezzo at specified timepoints after dosing.

Arithmetic mean plasma concentrations (ng/ml)[1]



[1] Under existing guidelines for generic products, generic versions of currently available zolpidem products may yield different blood levels than those presented.

[2] Average zolpidem plasma concentrations are from Transcept study ZI-15. In the CRL, FDA cited Leufkens et al., (2009), which studied driving effects of 10 mg zolpidem 5 to 6 hours after dosing.

[3] Average zolpidem plasma concentrations are as interpreted from the graph in the Ambien CR® Package Insert.

[4] Average Zolpimist®10mg plasma concentrations are as interpreted from the graph in the Package Insert.

[5] Average Edluar® 10 mg plasma concentrations are as interpreted from the graph in the Summary Basis of Approval.

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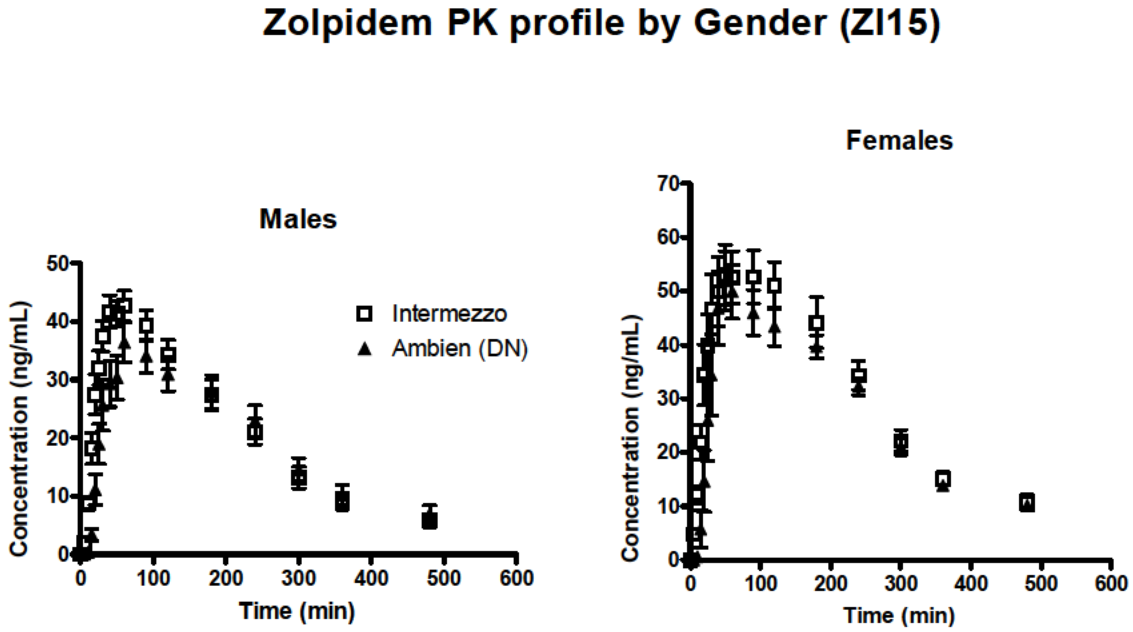
Reviewer's Comment:

Plasma zolpidem concentration in subjects is highly variable, in some studies the coefficient of variation observed was approximately 100%. Zolpidem plasma concentrations shown in the figure above are compared from studies conducted for different NDAs in different populations. Therefore based on high intra and inter study variability plasma concentration range approximately 2 fold is expected at any given time point.

Following Figure 2 represents analysis of PK profile of zolpidem by gender from study ZI15, a pivotal bioequivalence study comparing PK profiles of Intermezzo with reference Ambien®.

Analysis of zolpidem plasma concentration by gender indicates that females had approximately 30-40% higher plasma concentrations when compared to males.

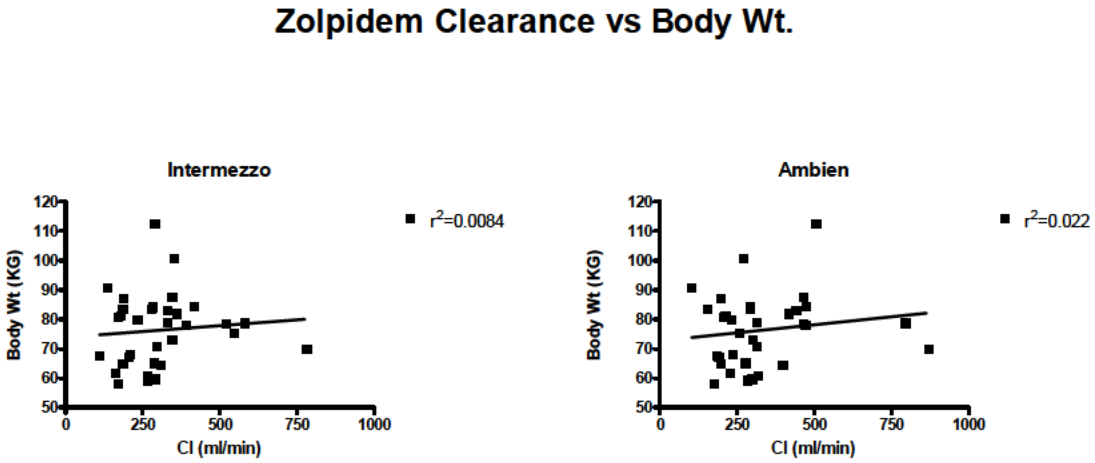
Figure 2: PK profile of zolpidem by gender from study ZI15, a pivotal bioequivalence study comparing PK profiles of Intermezzo with reference Ambien®.



Following Figure 3 represents analysis of PK profile of zolpidem by body-weight from study ZI15, a pivotal bioequivalence study comparing PK profiles of Intermezzo with reference Ambien®.

Analysis of zolpidem plasma concentration by body-weight indicates that there is no significant correlation between body-weight and zolpidem clearance when subjects were dosed with Intermezzo or Ambien®.

Figure 3: PK profile of zolpidem by body-weight from study ZI15



Zolpidem Plasma Concentration

Table 1 represents the number of male or female subjects with plasma concentrations greater than 30, 40 ng/mL at 3, 4, and 5 hours post dose (3.5 mg Intermezzo) from the PK studies conducted for the NDA 22-328 (Intermezzo).

Table 1: Number male or female subjects with zolpidem plasma concentrations greater than 30, 40 ng/mL at 3, 4, and 5 hours post dose

		Above 30 ng/mL Postdose			Above 40 ng/mL Postdose		
Study Number	**Number of Subjects**	**3 hrs**	**4 hrs**	**5 hrs**	**3 hrs**	**4 hrs**	**5 hrs**
ZI-05-009	M= 13	5	2	1	0	0	0
	F= 11	8	6	3	4	2	1
ZI13	M=23	11	4	1	2	0	0
	F=13	23	17	8	12	10	0
ZI14	M=9	7	5	4	4	2	1
	F=16	5	2	1	2	1	1
	Fasted						
ZI15	M=19	8	2	1	3	1	0
	F=15	13	10	2	8	2	0
	Fed						
	M=19	4	3	3	1	1	1

	F=15	6	5	4	1	0	0
ZI16	M=10	3	1	0	0	0	0
	F=20	17	12	10	10	9	7

Note: In study ZI13, a cross-over BE study, both treatments (IND formulation and commercial formulation) were considered.

Following tables represent the number of male or female subjects with plasma concentrations greater than 50, 60 ng/mL at 3, 4, and 5 hours post dose (3.5 mg Intermezzo).

Table 2: Number male or female subjects with zolpidem plasma concentrations greater than 50, 60 ng/mL at 3, 4, and 5 hours post dose

		Above 50 ng/mL Postdose			**Above 60 ng/mL Postdose**		
Study Number	**Number of Subjects**	**3 hrs**	**4 hrs**	**5 hrs**	**3 hrs**	**4 hrs**	**5 hrs**
ZI-05-009	M= 13	0	0	0	0	0	0
	F= 11	2	0	0	1	0	0
ZI13	M=23	0	0	0	0	0	0
	F=13	6	2	0	0	1	0
ZI14	M=9	0	0	0	0	0	0
	F=16	1	1	1	1	0	0
	Fasted						
ZI15	M=19	1	0	0	0	0	0
	F=15	2	1	0	2	0	0
	Fed						
	M=19	1	0	0	0	0	0
	F=15	0	0	0	0	0	0
ZI16	M=10	0	0	0	0	0	0
	F=20	9	6	5	6	3	1

Note: For study ZI13 both treatments (IND formulation and commercial formulation) were considered since they were BE.

The above two Tables show that greater proportion of the subjects with plasma concentration above 30, 40, 50 and 60 ng/mL at 3, 4, and 5 hours post dose are female indicating the gender difference in PK.

Analysis of Pharmacokinetic and Pharmacodynamic Data from New Drug Application Studies of Intermezzo

Objectives:

1. To identify the individual subjects in the top 10th percentile of the observed distributions of C_{max}, C_4, and total AUC.

2. Among individuals in the top 10th percentile group, identify factors potentially associated with the high exposure status. Factors available for analysis include: age, gender, weight, and race (ethnicity).

3. For pharmacodynamic (PD) studies, to identify individuals in the top 10th percentile of the observed distribution of placebo-normalized area under the PD effect curve for the Digit Symbol Substitution Test (DSST).

4. Among individuals in the top 10th percentile group, identify factors associated with the high response status.

5. In studies incorporating both PK and PD endpoints, evaluate whether individuals with high systemic drug exposure are the same as those with the greatest PD response.

Methods

Pharmacokinetic Pharmacodynamic Data
PK data were obtained from five separate clinical pharmacokinetic studies (see page 4) involving a total of 148 young volunteer subjects (aged 21-59 years) including 85 male and 63 female subjects. Study ZI-14 also included 23 elderly volunteers (aged 64-83 years), 9 male and 14 female.

In two of the studies (ZI-05-009 and ZI-17), PD measures were obtained concurrently with blood sampling. The present analysis was limited to the DSST. DSST was the only PD measure common to all the studies included in this NDA. DSST scores at each post-dosage time point were expressed as the change score relative to the pre-dose baseline score and placebo normalized. However, in study ZI-05-009 along with DSST, choice reaction time (CRT), symbol copying test (SCT), visual analytical score (VAS) were also obtained post dose.

In study ZI-16, DSST measures were available at multiple points after dosage, but the number of blood samples was limited to 3. A full PK analysis was not performed.

The area under the effect versus time curve was calculated for each individual. Based on the effect area distribution, individuals whose values were in the top 10th percentile (one of C_{max}, C_4, and total AUC) were identified.

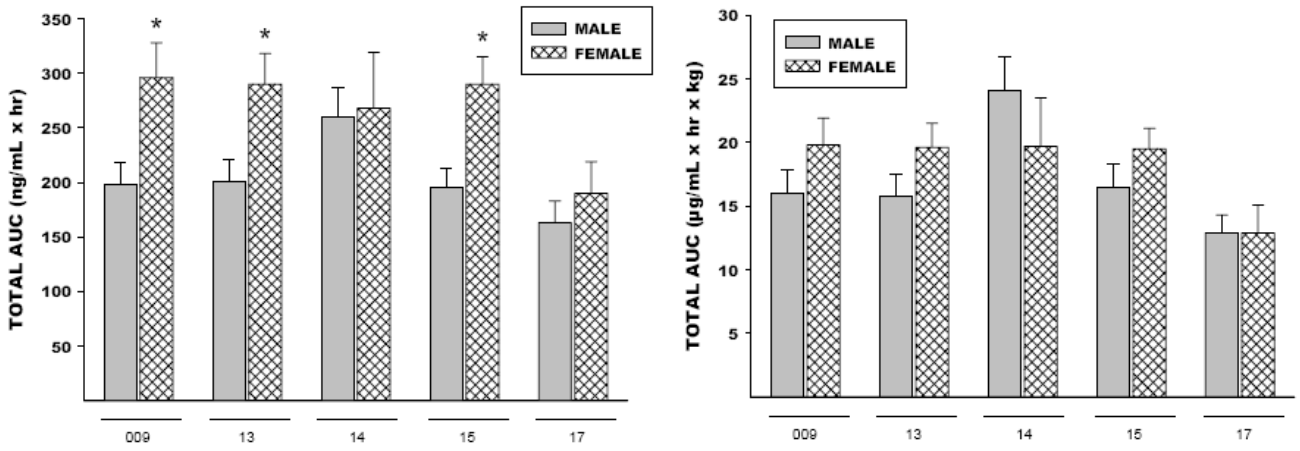
Subjects in the top 10th percentile in PD effect area were compared to those in the top 10th percentile in the pharmacokinetic analysis.

Effect of age on PD parameters was analyzed by stratifying age into two groups, subjects below 37.2 years and subjects above 37.2 years.

PK Analysis Results

The PK with-in subject variability measured as %CV was approximately 50% on an average among these five PK studies. The data indicates gender influences the pharmacokinetics of zolpidem. Cmax, C4, and AUC were significantly higher in women than those in men in many cases. The differences were partly explained by body weight. Weight normalized AUC was not significant in some cases (figure below), but, zolpidem concentration was still approximately 30% higher in female subjects in 3 out of 5 PK studies.

Figure 4: Mean (±SE) total AUC for zolpidem for male and female subjects in five separate studies



The Table below includes those subjects identified in top 10th % of PK parameters, Cmax, C4 and AUC. The 80% of the subjects identified in the top 10th percentile were females (20/25). Only 5/25 subjects were male (Table below).

Table 3: Subjects identified in top 10th percentile of PK analysis

	Gender	Age	Weight	Race	C_{max}	C_4	AUC 0-inf
Study ZI-05-009							
Group means: Male		32.5	80.3		53.2	20.1	198

Group means: Female		37.4	67.4		77.1	30.3	296
10th percentile subjects							
19	F	42	64.0	AA	102.8	35.4	342
23	F	33	59.0	White	126.0	49.2	463
24	F	38	67.8	White	98.6	46.6	448
Study ZI-13							
Group means: Male		28.8	78.6		55.6	38.7	201
Group means: Female		36.1	68.2		67.9	48.3	290
10th percentile subjects							
3	F	40	69.2	Unk.	93.6	61.1	466
6	F	28	58.4	White	108.1	80.6	636
13	F	51	84.9	White	73.5	63.6	356
22	F	52	44.2	White	96.0	40.5	244
23	F	20	66.8	White	84.9	65.6	422
Study ZI-14							
Group means: Male		30.5	92.3		59.8	26.4	260
Group means: Female		40.1	72.5		65.2	27.7	268
10th percentile subjects							
11	M	28	93.2	AA	90.7	45.5	539
17	F	42	70.0	White	90.1	51.2	565
45	F	34	62.7	White	99.1	45.7	412
Study ZI-15							
Group means: Male		29.9	83.6		50.7	21.1	195
Group means: Female		36.8	68.3		67.5	34.3	290
10th percentile subjects							
5	F	49	73.0	White	46.3	46.3	278
6	F	24	67.9	AA	80.4	34.8	281
17	F	21	50.7	White	91.8	55.4	531
21	F	34	61.5	White	81.4	35.2	363
23	M	30	90.5	AA	60.0	46.8	427
	Gender	Age	Weight	Race	Cmax	C4	AUC
Study ZI-16	(Sampling limited to 3 and 4 hours post dosage)						
Group means: Male		30.6	85.6		29.1	22.5	
Group means: Female		31.8	67.9		48.8	39.6	
10th percentile subjects							

3	F	31	46.7	White	83.8	65.2	
5	F	27	69.8	White	81.0	60.7	
10	F	31	61.2	White	73.3	68.6	
Study ZI-17							
Group means: Male		30.5	81.0		43.8	15.4	163
Group means: Female		32.1	67.4		43.8	21.7	190
10^{th} percentile subjects							
13	M	41	68.2	AA	96.9	20.9	243
14	F	22	80.5	AA	62.3	35.9	305
19	F	24	50.0	White	56.7	37.5	269
24	M	27	66.4	AA	23.0	17.7	583
30	M	27	74.1	AA	67.4	25.9	296
34	F	37	73.6	White	51.7	28.0	248

Reviewer's Comment:

Study ZI-05-009: Subject 023 identified in top 10^{th} percentile experienced treatment related nervous system related AEs including headache and dizziness.

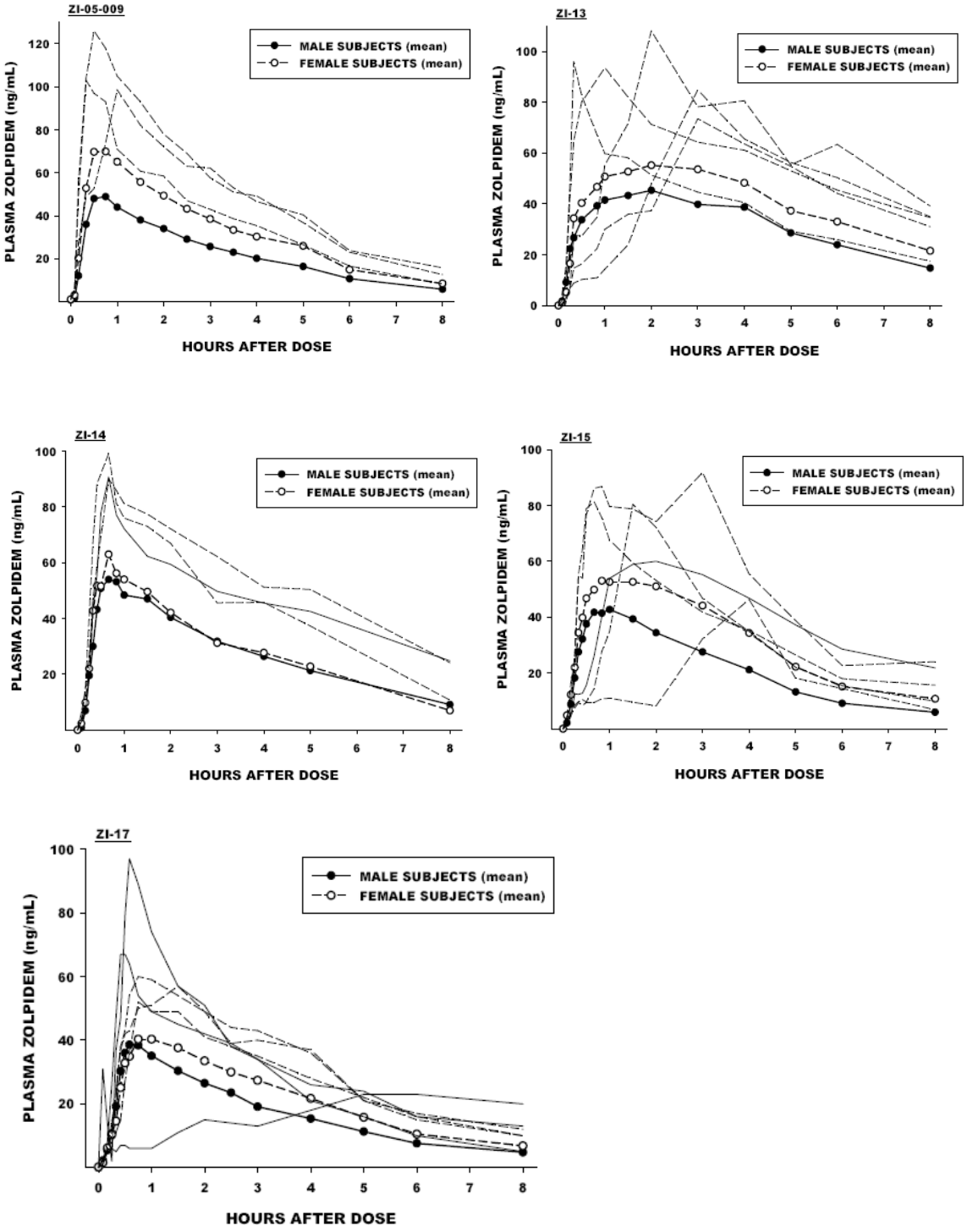
Study ZI13: Subject 003, 022 and 023 (all female subjects) identified in top 10^{th} percentile experienced treatment related nervous system related AEs including headache and dizziness.

Study ZI14: All the three subjects (subjects 011, 017 and 045) experiencing nervous system related AEs were identified in top 10^{th} percentile.

Study ZI15: None of the subjects identified in top 10^{th} percentile in the table above experienced nervous system related AEs.

Study ZI16: All the three subjects (subjects 003, 008 and 016) experiencing nervous system related AEs were females. Only, subject 003 was identified in top 10^{th} percentile.

Figure 5: Mean Plasma Concentrations and Profiles of Subjects identified in top 10^{th} percentile of PK analysis



Reviewer's Comment:

PK profiles of ZI-13 for males and females subjects shown in the figure above appears to be much different than the PK profile obtained in other studies (especially in terms of Cmax and tmax). However, PK profile of ZI-13 plotted from the original data set did not appear to be different when compared to other PK profiles as shown in the figure below.

Reviewer's Reanalysis:
Following PK profile of Study ZI-13 was plotted from the original data set for males and females combining plasma concentrations obtained for IND and commercial formulations.

Figure 6: Mean Zolpidem PK Profiles From Study ZI13 for Males and Females

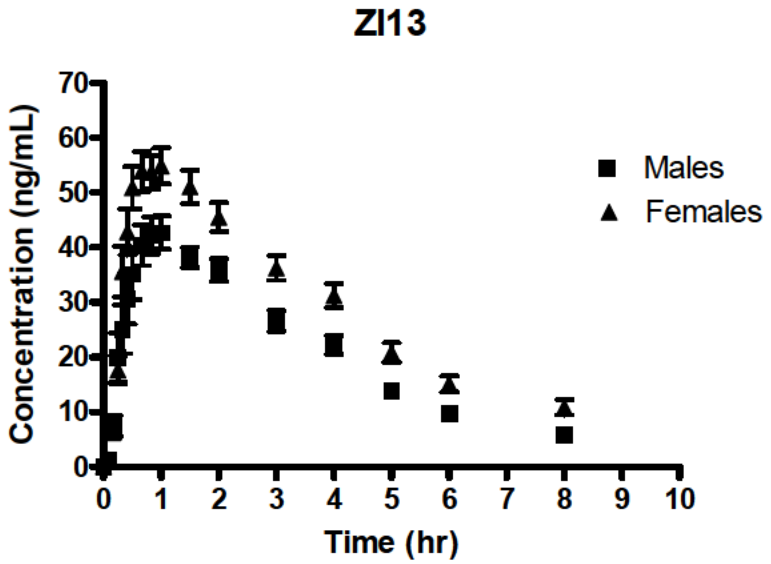


Table 4: Zolpidem Plasma Pharmacokinetic Parameters After Administration of Intermezzo 3.5 mg by Age, and Race

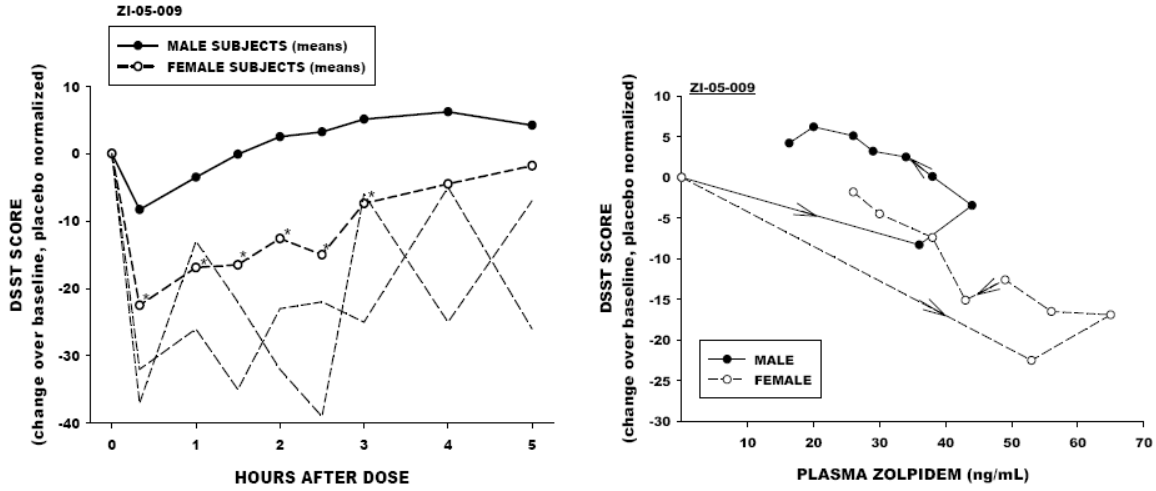
	Age < 37.2 Years (N=12)	Age >= 37.2 Years (N=12)	White (N=15)	Non-White (N=9)
Cmax (ng/mL)				
Mean (SD)	59.90 (22.49)	68.38 (22.36)	66.77 (21.90)	59.76 (23.73)
Median	54.36	66.72	58.13	56.56
Min, Max	38.57, 125.96	19.85, 102.81	47.78, 125.96	19.85, 102.81
Tmax (hr)				
Mean (SD)	0.631 (0.174)	0.632 (0.240)	0.655 (0.210)	0.592 (0.202)
Median	0.500	0.500	0.500	0.500
Min, Max	0.500, 1.000	0.330, 1.000	0.500, 1.000	0.330, 1.000
AUC0-inf (ng hr/mL)				
Mean (SD)	228.76 (94.50)	256.37 (108.25)	246.16 (98.12)	236.58 (109.77)
Median	208.22	247.88	206.32	229.46
Min, Max	117.61, 463.25	42.52, 448.16	117.61, 463.25	42.52, 388.69

Results from Pharmacodynamic and Pharmacokinetic Analysis

Study ZI-05-009

PD response to sublingual zolpidem, based on DSST scores, was greater in female subjects than that in males. Among females, placebo-normalized change scores differed significantly from no change, from times 0.33 through and including 3.0 hours after dosage. In male subjects, none of the change scores differed significantly from zero (Figure below, left). In the aggregate, gender differences in response were partly explained by higher plasma concentrations in women. The concentration-response relationship also differed between men and women, with greater sensitivity evident among the female subjects (Figure 7 below, right).

Figure 7: Mean DSST profile and DSST-plasma concentrations among men and women (ZI-05-009)



Asterisk (*) indicates a significant difference from zero change. Plots (dashed lines) for the top 10th percentile subject profiles included in the figure.

Right: Relation of mean plasma concentration to mean DSST change score for men and women. Arrows indicate the direction of increasing time.

Two subjects (2 and 18) with lower DSST score identified do not correspond to the subjects identified in top 10th percentile based on pharmacokinetics.

Table 5: Digital Symbol Substitution Test (DSST) Results - Number of Correct Substitutions by Time Point, Dose Group and Age

	Age < 37.2 Years (N=12)		Age >= 37.2 Years (N=12)	
	3.5 mg (N=12)	Placebo (N=12)	3.5 mg (N=12)	Placebo (N=12)
Pre-dose				
N	12	12	12	12

Mean (SE)	57.1 (4.26)	62.8 (3.87)	56.8 (3.40)	52.3 (3.86)
Median	55.0	63.0	56.0	47.5
Min, Max	36.0, 83.0	46.0, 91.0	41.0, 77.0	33.0, 78.0
20 min				
N	12	12	12	12
Mean (SE)	46.0 (4.88)	62.5 (3.64)	42.3 (3.58)	56.8 (3.46)
Median	47.0	60.5	44.0	56.0
Min, Max	17.0, 80.0	49.0, 88.0	24.0, 57.0	41.0, 76.0
Change[1] from Pre-dose at 20 min				
N	12	12	12	12
Mean (SE)	11.1 (4.55)	0.3 (1.93)	14.5 (2.45)	-4.4 (1.54)
Median	5.5	1.0	17.5	-2.0
Min, Max	-12.0, 41.0	-9.0, 14.0	1.0, 24.0	-15.0, 2.0
60 min				
N	12	12	12	12
Mean (SE)	52.4 (4.00)	63.2 (4.16)	46.7 (3.33)	56.5 (3.49)
Median	50.5	61.5	46.5	56.0
Min, Max	35.0, 87.0	43.0, 92.0	29.0, 70.0	39.0, 80.0
Change[1] from Pre-dose at 60 min				
N	12	12	12	12
Mean (SE)	4.7 (3.22)	-0.3 (1.11)	10.1 (2.07)	-4.2 (1.56)
Median	1.0	-0.5	10.0	-5.0
Min, Max	-11.0, 27.0	-6.0, 5.0	-2.0, 19.0	-10.0, 9.0
3 hr				
N	12	12	12	12
Mean (SE)	60.9 (4.84)	62.4 (3.88)	54.3 (3.72)	55.4 (2.95)
Median	57.5	61.5	49.5	54.5
Min, Max	33.0, 102.0	38.0, 87.0	38.0, 80.0	40.0, 72.0
Change[1] from Pre-dose at 3 hr				
N	12	12	12	12
Mean (SE)	-3.8 (3.64)	0.4 (1.81)	2.4 (2.57)	-3.1 (2.17)
Median	-3.5	2.0	-1.5	-2.5
Min, Max	-23.0, 21.0	-9.0, 10.0	-7.0, 20.0	-17.0, 7.0
4 hr				
N	12	12	12	12
Mean (SE)	59.0 (5.36)	60.8 (4.70)	57.9 (3.84)	54.9 (3.81)
Median	53.5	59.0	52.5	50.0
Min, Max	32.0, 100.0	39.0, 94.0	43.0, 79.0	41.0, 80.0
Change[1] from Pre-dose at 4 hr				
N	12	12	12	12
Mean (SE)	-1.9 (3.02)	2.1 (2.52)	-1.2 (3.15)	-2.6 (1.67)
Median	-1.0	2.5	0.0	-1.5
Min, Max	-17.0, 19.0	-11.0, 19.0	-32.0, 11.0	-13.0, 6.0

Table 6: Digital Symbol Substitution Test (DSST) Results - Number of Correct Substitutions by Time Point, Dose Group and Race

	White (N=15)		Non-White (N=9)	
	3.5 mg (N=15)	**Placebo (N=15)**	**3.5 mg (N=9)**	**Placebo (N=9)**
Pre-dose				
N	15	15	9	9
Mean (SE)	61.1 (3.54)	61.3 (3.76)	49.9 (2.82)	51.3 (3.86)
Median	60.0	57.0	48.0	47.0
Min, Max	41.0, 83.0	40.0, 91.0	36.0, 66.0	33.0, 67.0
20 min				
N	15	15	9	9
Mean (SE)	47.5 (3.71)	62.8 (3.42)	38.4 (4.65)	54.3 (3.05)
Median	51.0	60.0	36.0	50.0
Min, Max	24.0, 80.0	41.0, 88.0	17.0, 57.0	47.0, 75.0
Change[1] from Pre-dose at 20 min				
N	15	15	9	9
Mean (SE)	13.6 (3.33)	-1.5 (1.62)	11.4 (4.14)	-3.0 (2.30)
Median	16.0	-1.0	9.0	-3.0
Min, Max	-12.0, 41.0	-13.0, 14.0	-2.0, 34.0	-15.0, 7.0
60 min				
N	15	15	9	9
Mean (SE)	53.4 (3.55)	64.3 (3.21)	43.1 (2.69)	52.3 (4.07)
Median	49.0	60.0	45.0	47.0
Min, Max	30.0, 87.0	49.0, 92.0	29.0, 52.0	39.0, 77.0
Change[1] from Pre-dose at 60 min				
N	15	15	9	9
Mean (SE)	7.7 (2.66)	-3.0 (1.31)	6.8 (2.91)	-1.0 (1.62)
Median	9.0	-3.0	3.0	0.0
Min, Max	-11.0, 27.0	-10.0, 9.0	-5.0, 19.0	-10.0, 4.0
3 hr				
N	15	15	9	9
Mean (SE)	61.9 (4.12)	62.5 (3.03)	50.6 (3.52)	52.9 (3.67)
Median	58.0	61.0	50.0	55.0
Min, Max	38.0, 102.0	48.0, 87.0	33.0, 73.0	38.0, 72.0
Change[1] from Pre-dose at 3 hr				
N	15	15	9	9
Mean (SE)	-0.7 (3.06)	-1.2 (1.79)	-0.7 (3.52)	-1.6 (2.51)
Median	-1.0	1.0	-3.0	-3.0
Min, Max	-23.0, 20.0	-17.0, 10.0	-17.0, 21.0	-14.0, 8.0
4 hr				
N	15	15	9	9

Mean (SE)	64.8 (3.98)	62.1 (3.86)	47.9 (3.35)	50.8 (4.07)
Median	63.0	62.0	47.0	48.0
Min, Max	45.0, 100.0	45.0, 94.0	32.0, 70.0	39.0, 80.0
Change1 from Pre-dose at 4 hr				
N	15	15	9	9
Mean (SE)	-3.7 (2.89)	-0.7 (1.35)	2.0 (2.84)	0.6 (3.62)
Median	-2.0	1.0	0.0	-4.0
Min, Max	-32.0, 11.0	-11.0, 9.0	-10.0, 19.0	-13.0, 19.0

Following figures represent (mean± SD) DSST and other PD parameters measured in the study for all the subjects.

Figure 8: Mean DSST score change from predose by timepoint following administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo.

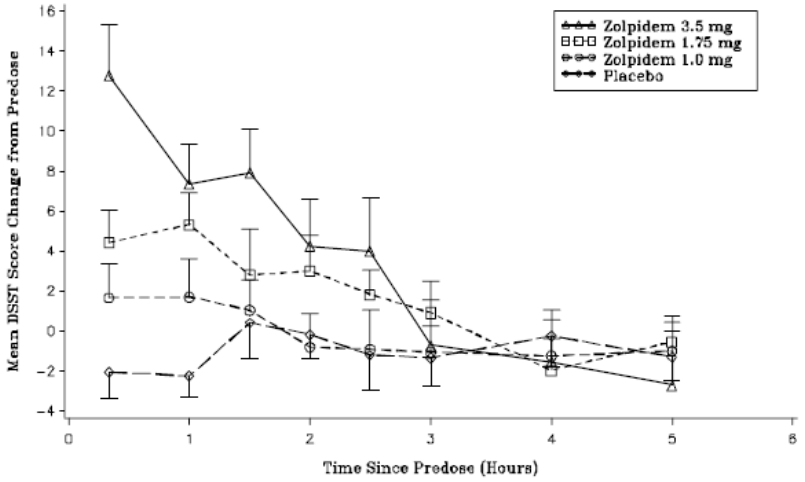
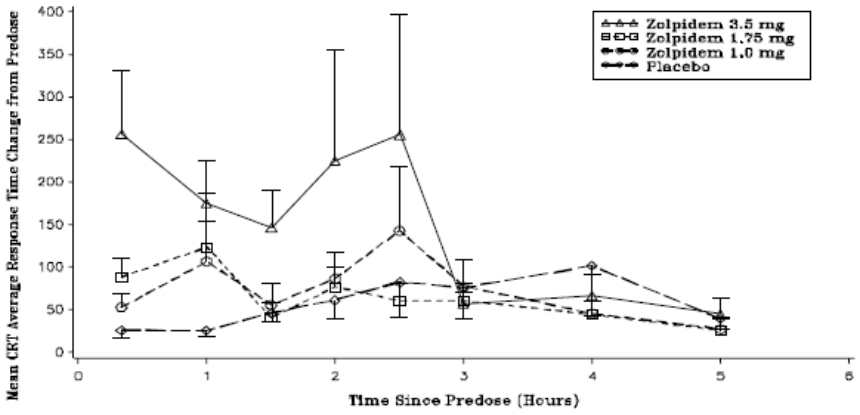


Figure 9: Mean Choice Reaction Time (CRT) average response time change from predose by timepoint following administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo.

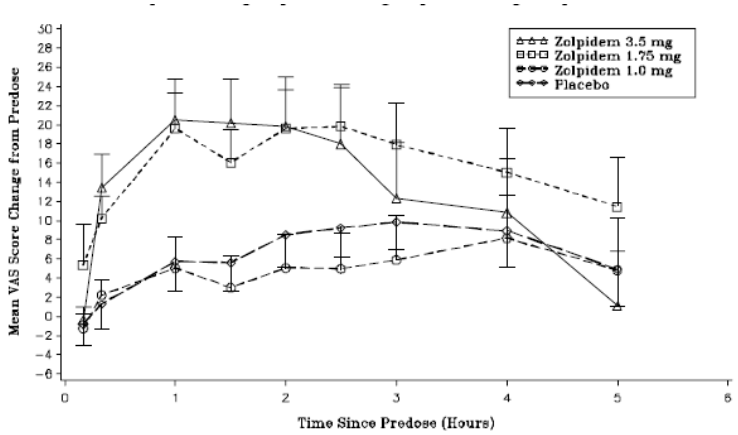


From the summary tables for CRT by gender, race and body weight:

Gender: CRT did not show any correlation with gender. However, during the initial sampling time points, females appeared to be more sensitive when compared to males. However, at 3 and 4 hr time points both groups were not significantly different from placebo.

CRT did not show any correlation with race or body weight.

Figure 10: Mean visual analog scale (VAS) score change from predose by timepoint after administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo.



From the summary tables for VAS by gender, race and body weight:

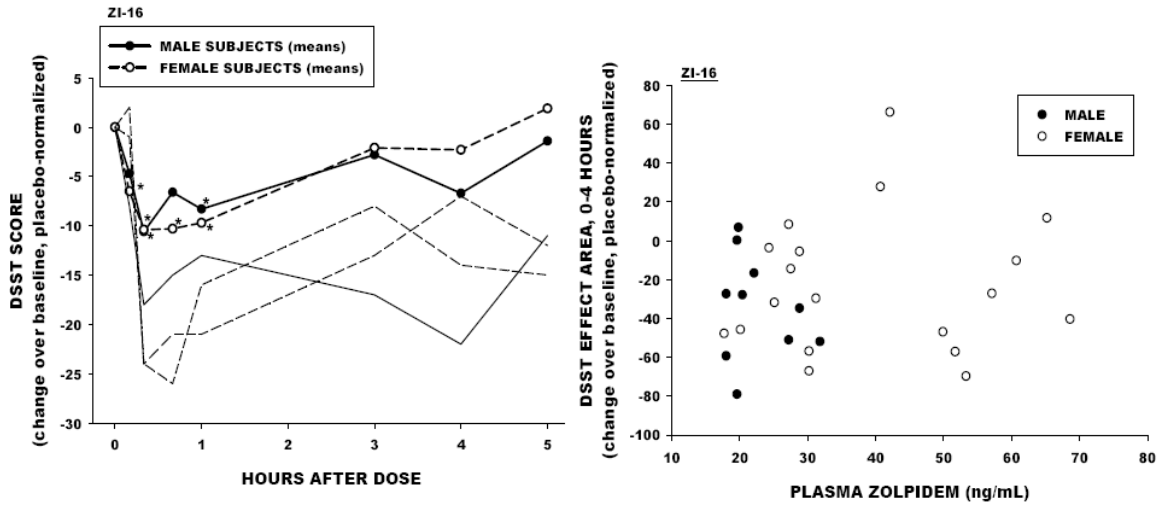
VAS did not show any correlation with gender, race or body weight.

Study ZI-16

In this study area under the 4-hour effect curve was similar between males and females in contrast to ZI-05-009. There were two females out of 3 subjects identified as top 10th percentile. Race or body weight did not show any trend in DSST evaluation.

Reviewer's Comment:
In this study, greater proportion of females showed higher plasma concentrations at 4 hrs postdose. However, DSST effect area did not show any correlation (i.e., females with higher zolpidem concentrations at 4 hours did not have highest change over baseline, Figure on right below).

Figure 11: Mean DSST profile and DSST (AUC_{0-4})-4 hour plasma concentrations for male and female subjects (ZI-16)



Left: Mean DSST scores for male and female subjects (ZI-16). Asterisk (*) indicates a significant difference from zero change.

Right: Relation of plasma concentration at 4 hours after dosage to area under the 4-hour effect curve for DSST

Table 7: Symbol Copying Test (SCT) Results - Number of Correct Copies by Time Point, Dose Group and Sex

	Male (N=13)		Female (N=11)	
	3.5 mg (N=13)	**Placebo (N=13)**	**3.5 mg (N=11)**	**Placebo (N=11)**
Pre-dose				
N	13	13	11	11
Mean (SE)	115.6 (11.92)	132.4 (6.63)	129.6 (6.50)	126.5 (6.95)
Median	122.0	131.0	127.0	131.0
Min, Max	0.0, 174.0	98.0, 173.0	101.0, 164.0	92.0, 164.0
20 min				
N	13	13	11	11
Mean (SE)	114.0 (8.73)	128.2 (6.28)	114.4 (8.74)	129.6 (7.54)
Median	120.0	127.0	103.0	124.0
Min, Max	61.0, 166.0	100.0, 174.0	87.0, 173.0	99.0, 171.0
Change[1] from Pre-dose at 20 min				
N	13	13	11	11
Mean (SE)	1.6 (11.96)	4.2 (2.88)	15.3 (7.34)	-3.1 (4.93)
Median	4.0	4.0	18.0	-6.0
Min, Max	-123.0, 60.0	-11.0, 24.0	-46.0, 49.0	-37.0, 19.0
60 min				
N	13	13	11	11
Mean (SE)	118.7 (7.57)	127.4 (6.98)	98.3 (8.75)	127.1 (6.94)
Median	123.0	127.0	96.0	127.0

Min, Max	79.0, 173.0	95.0, 170.0	35.0, 140.0	95.0, 166.0
Change1 from Pre-dose at 60 min				
N	13	13	11	11
Mean (SE)	-3.1 (11.34)	5.0 (2.12)	31.4 (6.27)	-0.5 (3.96)
Median	1.0	3.0	27.0	-4.0
Min, Max	-131.0, 37.0	-5.0, 20.0	3.0, 66.0	-17.0, 24.0
3 hr				
N	13	13	11	11
Mean (SE)	128.5 (6.62)	130.5 (5.37)	121.6 (7.79)	126.5 (8.24)
Median	124.0	125.0	119.0	120.0
Min, Max	82.0, 175.0	103.0, 172.0	95.0, 167.0	75.0, 163.0
Change1 from Pre-dose at 3 hr				
N	13	13	11	11
Mean (SE)	-12.9 (9.50)	1.9 (2.35)	8.0 (6.22)	0.0 (5.03)
Median	-2.0	1.0	5.0	-2.0
Min, Max	-123.0, 8.0	-14.0, 15.0	-18.0, 55.0	-32.0, 23.0
4 hr				
N	13	13	11	11
Mean (SE)	129.9 (6.70)	130.7 (6.68)	122.0 (7.32)	124.2 (7.32)
Median	129.0	127.0	110.0	124.0
Min, Max	78.0, 174.0	95.0, 175.0	97.0, 167.0	87.0, 166.0
Change1 from Pre-dose at 4 hr				
N	13	13	11	11
Mean (SE)	-14.3 (9.94)	1.7 (1.88)	7.6 (5.94)	2.4 (5.00)
Median	-4.0	2.0	2.0	4.0
Min, Max	-129.0, 8.0	-11.0, 14.0	-15.0, 50.0	-26.0, 39.0

Table 8: Subjects identified in top 10th percentile of PD response

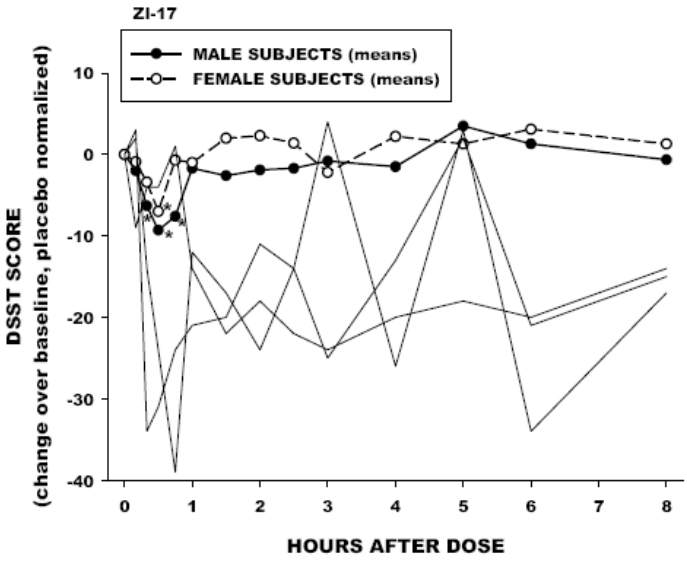
Subject	Gender	Age	Weight	Race
4	F	40	91.6	AA
11	M	27	81.6	White
15	F	42	71.6	White

These three subjects with lower DSST score identified do not correspond to the subjects identified in top 10th percentile based on pharmacokinetics.

ZI-17

Figure below shows mean values of DSST scores for men and women in the ZI-17. In this study mean values for men were slightly higher than females and in contrast to other studies all the subjects identified in top 10th percentile were male.

Figure 12: Mean placebo normalized DSST change scores among men and women (ZI-17)



Asterisk (*) indicates a significant difference from zero change.

Table 9: Subjects identified in top 10th percentile of PD response (ZI-17)

Subject	Gender	Age	Weight	Race
20	M	35	93.8	AA
23	M	22	86.4	White
31	M	22	73.0	White

These three subjects with lower DSST score identified do not correspond to the subjects identified in top 10th percentile based on pharmacokinetics.

Reviewer's Comments:

Driving study (ZI18) was conducted in response to CR letter for Intermezzo. But this study did not include PK sampling to determine the correlation between next day residual effects to zolpidem plasma concentration.

The PK and DSST (pharmacodynamic) analyses of studies conducted for Intermezzo could not explain safety issues (next day residual effects). The analysis had several limitations as listed below.

- Limited data is available to draw any meaningful conclusions to address next day residual effects.
- Systemic exposure was more variable (~50% CV) when compared DSST response variability.
- PD analysis was confined to DSST only, from all the studies. DSST is not considered as a validated biomarker to predict the next day residual effects for zolpidem. Study ZI-05-009 is the only one to measure the other PD parameters

including CRT, VAS, and symbol copying test (included in the summary tables). No consistent gender difference identified for these PD parameters.
- In one of the PK and PD study (ZI16) zolpidem plasma concentrations were measured at 3, 4 and 5 hours post dose only. Therefore complete PK analysis was not performed.

CONCLUSIONS

Based on the sponsor's analysis, it is concluded that:

- Subjects identified in top 10^{th} percentile in PK analysis did not correspond to the subjects identified in top 10^{th} percentile for DSST response.
- No correlation was seen for PK and DSST response with race and age (subjects divided into two age groups, below and above 37.2 years).
- DSST response in women was significantly higher when compared to men in Study ZI-15-009, but not in ZI16, ZI17. There is an uncertainty whether females are more sensitive to zolpidem.
- SCT obtained in Study ZI-05-009 showed that female subjects were more sensitive to the treatment when compared to males.
- Other PD parameters measured in study ZI-05-009 including CRT, VAS did not show any correlation with gender, race or body weight.
- On an average women had higher systemic exposure (upto 50% more) when compared to males following administration of 3.5 mg Intermezzo tablets. These differences remained partly after correction for body weight.

Based on the reviewer's analysis, it is concluded that:

- Zolpidem plasma concentrations in females was 30-40% higher in females when compared to males in the pivotal BE study ZI15.
- There was no significant correlation between Zolpidem clearance and body-weight.
- Plasma concentration above 30, 40, 50 and 60 ng/mL at 3, 4, and 5 hours post dose were seen mostly in female subjects indicating the gender differences and possible next day residual effects in these subjects.
- There is no correlation between PK and PD for next day residual effects identified.

RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP1) has reviewed the PK/PD analysis of NDA 22-328. This submission could not identify the possible causes for subjects showing next day residual effects seen in driving study based on analysis of submitted PK or DSST data. Further data need to be collected to justify the dose selection to avoid the severe adverse events (e.g, next day residual effects.)

Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

Angela Men, M.D., Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 NDA# 22-328
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Mohan Parepally

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

/s/

JAGAN MOHAN R PAREPALLY
07/07/2011

YUXIN MEN
07/07/2011

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Zolpidem Tartrate
NDA:	22-328
SUBMISSION DATE	9/30/2008
PRODUCT (Brand Name):	Intermezzo®
DOSAGE FORM:	Sublingual Tablet
DOSAGE STRENGTHS:	1.75 and 3.5 mg
INDICATION:	As-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN)
NDA TYPE:	505 (b)(2)
SPONSOR:	Transcept Pharma Inc.
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class for the short term treatment of insomnia characterized by difficulties with sleep initiation. Oral tablets of zolpidem tartrate are currently marketed under trade name of Ambien®. Intermezzo® is a sublingual tablet formulation of zolpidem tartrate. The proposed indication is as-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN). The current 505(b)(2) NDA seeks approval of Intermezzo® 1.75 mg and 3.5 mg sublingual tablet form of zolpidem tartrate. The 3.5 mg dose of the zolpidem tartrate sublingual tablet is the proposed dose for patients older than 18 years but less than 65 years of age, whereas the 1.75 mg dose is the recommended dose for patients older than 65 years and patients with compromised hepatic function.

Clinical safety and efficacy of the zolpidem tartrate sublingual tablet is supported by 2 well-controlled studies that provide evidence of efficacy for the intended claim. This NDA includes three single dose placebo controlled pharmacodynamic studies in healthy subjects (study ZI-05-009, ZI-16 and ZI-17). The NDA also contains studies specifically requested by the Agency to address food effect, relative bioavailability (versus the reference-listed drug, Ambien®), and determine the pharmacodynamic (PD) effects of immediate swallowing Vs delayed swallowing of the tablet.

This NDA also comprises of the following 3 single-dose pharmacokinetic (PK)/ bioequivalence (BE) bridging studies in healthy adult and elderly subjects. Study ZI-15, provides comparative bioavailability information relative to reference Ambien®. Study ZI-14 includes comparative bioavailability of Intermezzo® 1.75 mg and 3.5 mg in elderly and adult cohorts. Study ZI-13 provides a bridging link between IND formulation and final commercial formulation used in different studies. Final commercial formulation was used in most of the studies including pivotal BE, pharmacodynamic, and efficacy studies.

Food effect on pharmacokinetic profile of zolpidem after sublingual administration was evaluated in study ZI-15. A statistically significant lower bioavailability was observed for sublingual zolpidem with meal compared to sublingual zolpidem under fasting conditions, similar to other zolpidem products including the reference Ambien®.

In addition to this, the submission also contained 4 pilot studies; these studies were conducted before initiation of IND. Studies include ZI-04-001-001, ZI-04-002-002, ZI-04-003-003, ZI-04-007. In all the above studies higher doses (10 mg) of zolpidem were used.

A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 22-328. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view pending agreement of labeling recommendations in the package insert.

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

Clinical Pharmacology briefing was held on 06/15/09 and the attendees were Drs. Mehul Mehta, Ramana Uppoor, Veneeta Tandon, Ronald Farkas and Ting Ong.

B. Phase IV Commitments

None.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

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

Relative Bioavailability*:* Sponsor has conducted a relative bioavailability study comparing proposed commercial formulation with the reference Ambien® (Study ZI-15). Comparison of pharmacokinetic parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max}) under fasting conditions for 3.5 mg sublingual zolpidem tartrate tablet vs. 10 mg oral zolpidem tartrate (Ambien®) tablet indicate that the systemic exposure ($AUC_{0\text{-}inf}$ and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate tablet is well within the exposure of a 10 mg oral zolpidem tartrate tablet (Ambien®).

Sponsor has also conducted a bioequivalence study comparing proposed commercial formulation with the IND formulation used during the development, to provide a bridging link between IND formulation and proposed commercial formulation in Study ZI-13. IND formulation was bioequivalent to the proposed commercial formulation.

The overall conclusions from the comparative pharmacokinetic studies are summarized below:

Study ZI-15: This study was conducted to compare relative bioavailability between final commercial formulation and the reference Ambien®.

Following table provides the primary pharmacokinetic parameter ratios and 90% confidence intervals based on sponsor's analysis.

Table 1: Analysis of Relative Bioavailabity of 3.5 mg Sublingual Zolpidem Tartrate Tablet and 10 mg Oral Ambien® Under Fasted Conditions (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
3.5 mg Intermezo® Fasting/10 mg Ambien® Fasting	AUC_{0-t}	38.2	35.88	40.67
	$AUC_{0-\infty}$	37.8	34.72	41.15
	C_{max}	39.28	34.73	44.43

According to the sponsor's analysis, ANOVA detected a statistically significant difference between treatments for AUC_{0-inf} and Cmax.

The results indicate that the systemic exposure (AUC_{0-inf} and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate tablet is well within the exposure to zolpidem after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) which was found to be safe.

Study ZI-13: This study was conducted to establish bioequivalence bridging link between IND formulation and the proposed commercial formulation.

Bioequivalence criteria were met between commercial formulation and IND formulation under fasting conditions. The geometric mean ratio of commercial formulation and IND formulation for the $AUC_{0-\infty}$ was 109.2 with 90% CI = (103.3, 115.3). Cmax geometric mean ratio was 102.9 with 90% CI = (93.9, 112.8).

Table 2: Bioequivalence Analysis: Proposed Commercial Formulation 3.5 mg Sublingual Zolpidem Tartrate Tablet (A) vs IND Formulation 3.5 mg Sublingual Zolpidem Tartrate tablet (B) (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI	Intra-Subject CV
Commercial Formulation / IND Formulation	AUC_{0-t}	109.0	103.4	115.1	12.7%
	$AUC_{0-\infty}$	109.2	103.3	115.3	13.0%
	C_{max}	102.9	93.9	112.8	21.8%

Food Effect: Food effect on pharmacokinetic profile of zolpidem after sublingual administration was evaluated using final commercial formulation in study ZI-15. The 90% CI for the effect of food on the Intermezzo® is shown in the following table.

Table 3: Food Effect Assessment Summary (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90%	Upper 90%	Intra-Subject

			CI	CI	CV%
3.5 mg Intermezo® Fed/3.5 mg Intermezzo® Fasting	AUC_{0-t}	81.04	76.12	86.27	15.27
	$AUC_{0-\infty}$	104.03	95.37	113.49	20.76
	C_{max}	57.77	51.1	65.32	30.47

The peak plasma concentration (C_{max}) decreased by approximately 38% and AUC_{0-t} decreased by 19% on an average (arithmetic mean), following administration with food. Consumption of a standard high-fat breakfast within 30 minutes of administration of the 3.5 mg sublingual zolpidem tartrate tablet delayed time to reach the peak concentration (T_{max}) from 1 hour in the fasted state to ~3 hours in the fed state. Mean values (% CV) for the T_{max} were 1.21 h (70.02%) under fasting conditions and 2.71 h (63.66%) under fed conditions. Food decreased bioavailability and delayed Tmax of sublingual zolpidem similar to other zolpidem products including the reference Ambien®.

Exposure in Elderly Population: Sponsor has provided information on bioavailability of 1.75 mg and 3.5 mg sublingual zolpidem in healthy elderly cohort and 3.5 mg sublingual zolpidem in healthy adult cohort in Study ZI-14. Exposure to zolpidem from 1.75 mg and 3.5 mg sublingual zolpidem was dose proportional under fasting conditions in elderly cohort. Mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher in elderly subjects compared to Adults.

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative-hypnotic drugs and the difference in the exposure to zolpidem is a concern in the treatment of elderly. Therefore the recommended dose in elderly is half the adult dose (1.75 mg) similar to other zolpidem products including the reference Ambien®.

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

Table 4: 1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A) vs 3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B) (Dose normalized data, Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI	Intra-Subject CV
1.75 mg Sublingual Zolpidem Tartrate/ 3.5 mg Sublingual Zolpidem Tartrate	AUC_{0-t}	103.6	98.4	109.0	9.88%
	$AUC_{0-\infty}$	104.5	99.3	109.9	9.69%
	C_{max}	95.88	88.9	103.4	14.6%

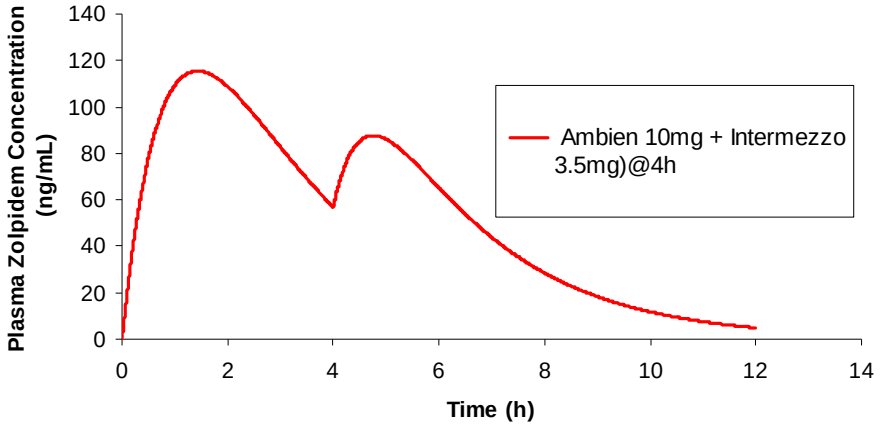
Table 5: Following table represents PK parameters and comparison between elderly and adult subjects receiving 3.5 mg sublingual zolpidem

		3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B)			3.5 mg Sublingual Zolpidem Tartrate Tablet (Adult Non-Elderly Cohort) (B)			
Parameters		**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**	**Means Ratio % (Elderly/ Adult)**
AUC0-inf	(ng·h/mL)	352.45	187.94	53.32	262.99	121.04	46.02	134.0
Cmax	(ng/mL)	83.10	25.04	30.14	61.87	15.77	25.50	134.3

Potential Effects of Re-Dosing: The mean zolpidem plasma concentration time profile indicates that the maximum plasma concentration (Cmax) attained after a single dose administration of 3.5 mg zolpidem sublingual tablet was approximately 47 ng/mL. At approximately 6 hrs and 33 minutes, plasma concentration of zolpidem would be 10% of Cmax. Zolpidem plasma concentration after 3 and 4 hrs would be approximately 25.6 ng/mL or 54% of Cmax and 16.1 ng/mL or 34% of Cmax respectively.

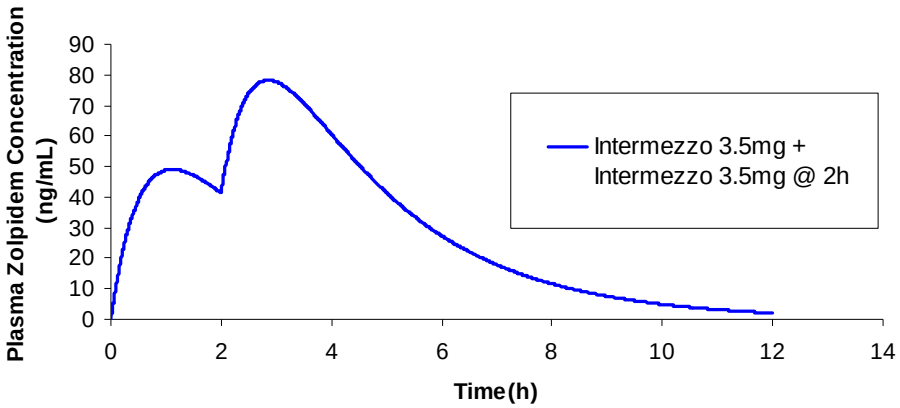
The predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of zolpidem (as 3.5 mg sublingual tablet) following first 10 mg dose (Ambien®) separated by 4 hrs were 65.2, 28.5 and 11.7 ng/mL respectively as shown in the figure below.

Predicted zolpidem plasma concentration time profile



Predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of 3.5 mg sublingual tablet following first 3.5 mg dose separated by 2 hrs were 60.4, 27.3 and 11.6 ng/mL respectively as shown in the figure below.

Predicted zolpidem plasma concentration time profile

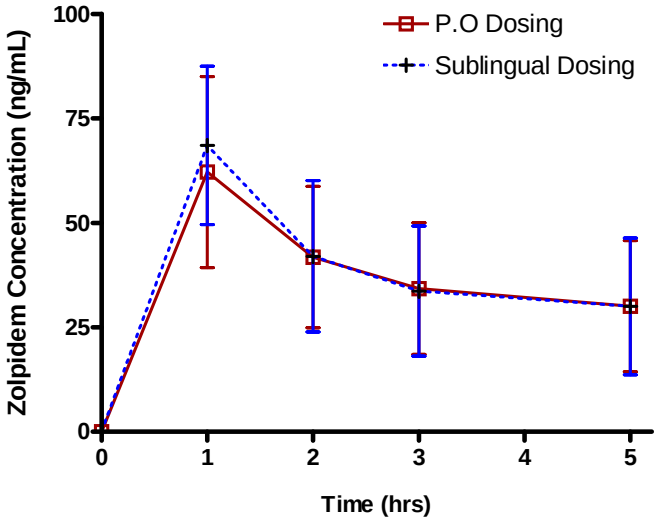


In a pharmacodynamic study ZI-16 with Intermezzo DSST scores were evaluated for sublingual and oral (immediate swallowing) administration in comparison with placebo treatment. Pharmacokinetic samples were also taken at 0, 1, 2, 3, and 5 hours. DSST scores returned to the baseline within 3- 4 hrs postdose corresponding to 30 ng/mL approximate mean plasma zolpidem concentration.

Pharmacodynamic effects may be comparable to that of placebo beyond 4 hours of second dose in this case of potential re-dosing in the above scenarios.

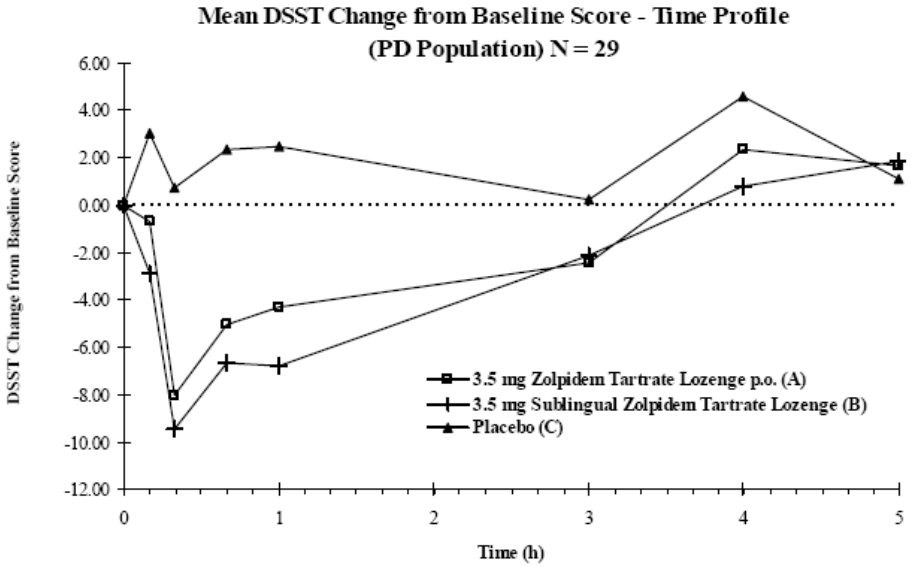
Sublingual Administration vs Swallowing: Study ZI-16 compared hypnotic effects (digital symbol substitution test, DSST) of sublingual tablet formulation with placebo and same formulation after immediate swallowing (p.o dosing). Five blood samples were taken to measure zolpidem plasma concentrations. Following figure represents PK profiles for sublingual and p.o dosing. Pharmacokinetic profiles appeared to be similar for sublingual and p.o dosing. PK sampling time points were inadequate to quantitate the absorption differences between sublingual and oral administration.

Mean (SD) plasma zolpidem concentrations time profile obtained after sublingual and p.o dosing.



There were no statistically significant differences between 3.5 mg zolpidem tartrate lozenge p.o. and 3.5 mg sublingual zolpidem tartrate lozenge in any of the PD parameters. However, area under DSST change from base line score appeared to be more for sublingual administration.

Following figure represents mean DSST change from baseline score in different treatment groups.



Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

Ramana Uppoor, Ph.D. Date
Deputy Director/Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 NDA 22-328
HFD-860 Mehul Mehta, Ramana Uppoor, Veneeta Tandon, Jagan Parepally

II. QUESTION BASED REVIEW

General Attributes

Drug/Drug Product Information:

Dosage Form/Strengths: Intermezzo® is a sublingual tablet formulation of zolpidem tartrate. The composition of the proposed commercial formulation is shown in the following table.

Table 6: Composition of Zolpidem Tartrate Sublingual Tablets

Ingredient	Grade	Function	1.75 mg		3.5 mg	
			mg	(b) (4)	mg	(b) (4)
Zolpidem Tartrate	-	Active Substance	1.75		3.5	
(b) (4)	Supplier's Grade	(b) (4)			(b) (4)	
	Supplier's Grade					
Croscarmellose Sodium	USP/NF					
Sodium Stearyl Fumarate	USP/NF					
Silicon Dioxide	USP/NF					
Natural and Artificial Spearmint Flavor	Supplier's Grade					
Silicon Dioxide Colloidal- (b) (4)	USP/NF					
Iron Oxide Beige	Supplier's grade					
Sucralose	USP/NF					
Iron Oxide Yellow	USP/NF					
Total Tablet Weight/Percent	-	-	210.00		210.00	

Indication: Intermezzo® (zolpidem tartrate) is indicated for as-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN).

What is the proposed mechanism (s) of action?

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. Zolpidem *in vitro* binds the (BZ_1) receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. The (BZ_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (BZ_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (Stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

A. General Clinical Pharmacology

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

The clinical trials conducted by the sponsor to support the approval of the Intermezzo® are summarized in the following table:

Table 7: Clinical trials in support of the Intermezzo®

Type of Study and Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients	Duration of Treatment

BE ZI-13	Formulation bridging PK study	Randomized, open-label, two-period crossover	Zolpidem tartrate sublingual tablet, 3.5 mg (IND formulation); sublingual Zolpidem tartrate sublingual tablet, 3.5 mg (proposed commercial formulation); sublingual	Healthy Subjects (n=36)	Single doses
PK ZI-14	PK, safety and tolerability of 2 doses of zolpidem tartrate sublingual tablets in elderly vs. non-elderly	Randomized, open-label, 2-way crossover for elderly (no crossover for non-elderly)	Zolpidem tartrate sublingual tablet, 1.75 mg (elderly); sublingual Zolpidem tartrate sublingual tablet, 3.5 mg (elderly); sublingual Zolpidem tartrate sublingual tablet, 3.5 mg (non-elderly); sublingual	Healthy elderly and non-elderly adult subjects (n=24)	Single dose
PK ZI-15	Evaluate effect of food on PK plus comparative PK for zolpidem tartrate sublingual tablet vs. Ambien® 10 mg	Randomized, open-label, 3-period, 6-sequence crossover	Zolpidem tartrate sublingual tablet, 3.5 mg (fed); sublingual Zolpidem tartrate sublingual tablet, 3.5 mg (fasted); sublingual Ambien®, 10	Healthy Subjects (n=36)	Single dose

			mg tablet (fasted); oral		
PK/PD ZI-05-009	Evaluate PK/PD, safety and dose proportionality of 3 doses of zolpidem tartrate sublingual tablet vs. placebo	Randomized, double-blind, daytime, placebo-controlled, 4-way crossover	Zolpidem tartrate sublingual tablet, 1.0, 1.75 and 3.5 mg; sublingual Placebo tablet; sublingual	Healthy Subjects (n=24)	Single doses given on 2 consecutive days
PD ZI-16	Evaluate comparative PD effects and late PK effects of sublingual vs. oral zolpidem tartrate sublingual tablet dosing	Randomized, double-blind, 3-period, 6-sequence crossover	Zolpidem tartrate sublingual tablet, 3.5 mg; oral Zolpidem tartrate sublingual tablet, 3.5 mg ; held under tongue for 2 min Placebo; sublingual or oral	Healthy Subjects (n=30)	Single dose
PK/PD ZI-17	Evaluate comparative early PK/PD parameters between sublingual vs. oral dosing	Part I: Randomized, DB, double-dummy, placebo-controlled 3-way, 6-	Part I: Zolpidem tartrate sublingual tablet, 3.5 mg; sublingual Zolpidem tartrate, 3.5 mg	Healthy Subjects (n=36)	Single dose

		sequence crossover Part II: Randomized, open-label, single dose	tablet; oral Placebo; sublingual or oral Part II: Ambien®, 10 mg tablet; oral		
Efficacy and Safety ZI-06-010	Efficacy and safety of 2 doses of zolpidem tartrate sublingual tablet vs. placebo in a sleep lab with scheduled awakening (objective and subjective measures)	Randomized, double-blind, placebo-controlled 3-way crossover	Zolpidem tartrate sublingual tablet, 1.75 and 3.5 mg; sublingual Placebo tablet; sublingual	Adult patients with insomnia characterized by difficulty returning to sleep after MOTN Awakening (n=82)	Single doses given on 2 consecutive nights
Efficacy and Safety ZI-12	Efficacy and safety of zolpidem tartrate sublingual tablet vs. placebo; (subjective measures) in an out-patient setting with as needed dosing over 28 days	Randomized, double-blind, parallel group, placebo-controlled	Zolpidem tartrate sublingual tablet, 3.5 mg; sublingual Placebo tablet; sublingual	Adult patients with insomnia characterized by difficulty returning to sleep after MOTN awakening (n=295)	4 weeks prn dosing

Sponsor has also conducted four pilot studies ZI-04-001-001, ZI-04-002-002, ZI-04-003-003 and ZI-04-007-007.

B. Intrinsic Factors

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

Exposure in Geriatric Population

Sponsor has provided information on bioavailability of 1.75 mg and 3.5 mg sublingual zolpidem in healthy elderly cohort and 3.5 mg sublingual zolpidem in healthy adult cohort in Study ZI-14. Exposure to zolpidem from 1.75 mg and 3.5 mg sublingual zolpidem was dose proportional under fasting conditions in elderly cohort. Mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher in elderly subjects compared to Adults.

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

Table 8: 1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A) vs 3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B) (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI	Intra-Subject CV
1.75 mg Sublingual Zolpidem Tartrate/ 3.5 mg Sublingual Zolpidem Tartrate	AUC_{0-t}	103.6	98.4	109.0	9.88%
	$AUC_{0-\infty}$	104.5	99.3	109.9	9.69%
	C_{max}	95.88	88.9	103.4	14.6%

Table 9: Following table represents PK parameters and comparison between elderly and adult subjects receiving 3.5 mg sublingual zolpidem

		3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B)			3.5 mg Sublingual Zolpidem Tartrate Tablet (Adult Non-Elderly Cohort) (B)			
Parameters		**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**	**Means Ratio % (Elderly/ Adult)**
AUC0-inf	(ng·h/mL)	352.45	187.94	53.32	262.99	121.04	46.02	134.0
Cmax	(ng/mL)	83.10	25.04	30.14	61.87	15.77	25.50	134.3

C. Extrinsic Factors

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

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

D. General Biopharmaceutics

What is the formulation of Intermezzo® sublingual tablet

The sponsor has developed a sublingual tablet formulation containing the active ingredient zolpidem tartrate at two dosage strengths, 1.75 and 3.5 mg. Dosage strengths 1.75 and 3.5 mg are (b) (4)

Two different formulations were used during the clinical development of Intermezzo® including IND formulation and proposed commercial formulation. IND formulation was shown to be bioequivalent to proposed commercial formulation in the Study ZI-13.

Is relative bioavailability of Intermezzo® comparable to Ambien® tablets in healthy subjects?

Sponsor has conducted a relative bioavailability study comparing proposed commercial formulation with the reference Ambien® (Study ZI-15). Comparison of pharmacokinetic parameters (AUC0-inf, AUC0-t and Cmax) under fasted conditions for 3.5 mg sublingual zolpidem tartrate tablet vs. 10 mg oral zolpidem tartrate (Ambien®) tablet indicate that the systemic exposure ($AUC_{0\text{-}inf}$ and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate lozenge is lower than the exposure after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) that was found to be safe.

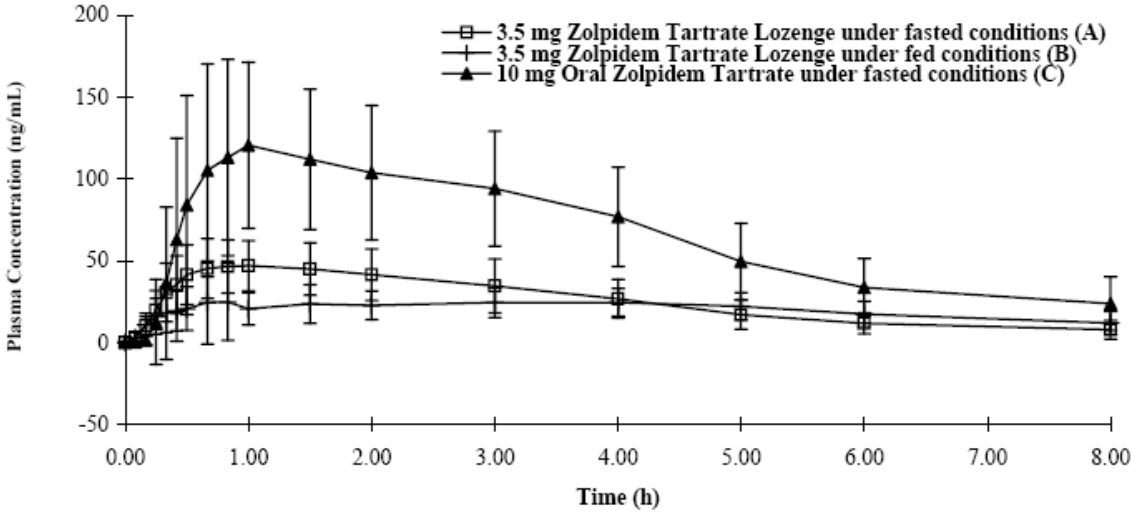
The overall conclusions from the comparative pharmacokinetic study are summarized below:

Study ZI-15: This study was conducted to compare relative bioavailability between final commercial formulation and the reference Ambien®.

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

Figure 1: Mean zolpidem (± SD) plasma concentrations (ng/mL) vs time profiles

Figure 2a: Zolpidem Mean Concentration - Time Profile
N = 33



Following table indicates the PK parameters for different treatments.

Table 10: Sponsor's Summary of Pharmacokinetic Results – 3.5 mg Sublingual Zolpidem Tartrate Tablet (N = 33) and 10 mg Oral Ambien® Under Fasted Conditions

		3.5 mg Sublingual Zolpidem Tartrate Tablet under Fasted			10 mg Oral Zolpidem Tartrate Tablet (Ambien®) under Fasted		
Parameters	**Units**	**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	201.40	74.29	36.89	525.29	188.09	35.81
AUC0-inf	(ng·h/mL)	231.41	100.06	43.24	620.71	281.80	45.40
AUC0-4h	(ng·h/mL)	145.48	48.36	33.24	362.85	124.59	34.34
AUCt/inf	(%)	89.10	6.16	6.92	87.31	7.50	8.59
AUC0-15 min	(ng·h/mL)	1.91	1.04	54.57	0.64	1.28	200.37
AUC0-20 min	(ng·h/mL)	3.97	2.02	50.80	2.68	4.18	156.25
AUC0-[25 ng/mL]	(ng·h/mL)	6.82	7.32	107.34	7.48	14.75	197.28
AUC0-1h	(ng·h/mL)	32.59	12.22	37.51	67.32	38.58	57.31
AUC0-[Tmax]	(ng·h/mL)	41.61	42.05	101.05	73.26	69.44	94.79
C15 min	(ng/mL)	19.85	11.88	59.88	12.49	25.96	207.82
C20 min	(ng/mL)	30.48	17.94	58.86	36.11	46.49	128.77
Cmax	(ng/mL)	57.18	15.88	27.76	146.60	50.91	34.73

Tmax (Mean)	(h)	1.21	0.85	70.02	1.18	0.86	73.25
Tmax (Median)	(h)	1.00	0.83	N/AP	0.833	0.600	N/AP
T1/2max	(h)	0.450	0.434	96.45	0.583	0.418	71.64
T[25 ng/mL]	(h)	0.516	0.509	98.70	0.562	0.512	91.16
Kel	(h^{-1})	0.3327	0.0873	26.24	0.3204	0.0826	25.77
T½ el	(h)	2.23	0.61	27.13	2.33	0.74	31.77

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

Table 11: Relative Bioavailability Assessment Between 3.5 mg Sublingual Zolpidem Tartrate Tablet and 10 mg Oral Ambien® Under Fasted Conditions (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
3.5 mg Intermezo® Fasting/10 mg Ambien® Fasting	AUC_{0-t}	38.2	35.88	40.67
	$AUC_{0-\infty}$	37.8	34.72	41.15
	C_{max}	39.28	34.73	44.43

According to the sponsor's analysis, ANOVA detected a statistically significant difference between treatments for AUC_{0-inf} and Cmax.

The results indicate that the systemic exposure (AUC_{0-inf} and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate tablet is well within the exposure to zolpidem after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) which was found to be safe.

What is the effect of food on the bioavailability of Intermezzo®?

Food significantly lowers bioavailability of sublingual zolpidem when compared to sublingual zolpidem under fasting conditions. Food effect on pharmacokinetic profile of zolpidem after sublingual administration was evaluated using final commercial formulation in study ZI-15. The peak plasma concentration (C_{max}) decreased by approximately 38% and AUC_{0-t} decreased by 19% on an average, following administration with food. Consumption of a standard high-fat breakfast within 30 minutes of administration of the 3.5 mg sublingual zolpidem tartrate tablet delayed time to reach the peak concentration (T_{max}) from 1 hour in the fasted state to ~3 hours in the fed state. Mean values (% CV) for the T_{max} were 1.21 h (70.02%) under fasting conditions and 2.71 h (63.66%) under fed conditions. Food decreased bioavailability and delayed Tmax of sublingual zolpidem similar to other zolpidem products including the reference Ambien®.

Following table represents PK parameters of sublingual zolpidem under fasting and fed conditions. Please refer to figure 2, treatment B for PK profile.

Table 12: Summary of Pharmacokinetic Results – 3.5 mg Sublingual Zolpidem Tartrate Tablet Under Fasting and Fed Conditions

Parameters		**3.5 mg Sublingual Zolpidem Tartrate Tablet under Fasted**			**3.5 mg Sublingual Zolpidem Tartrate Tablet under Fed**		
		Mean	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	201.40	74.29	36.89	160.77	54.39	33.83
AUC0-inf	(ng·h/mL)	231.41	100.06	43.24	259.70	216.24	83.27
Cmax	(ng/mL)	57.18	15.88	27.76	35.63	23.72	66.58
Tmax (Mean)	(h)	1.21	0.85	70.02	2.71	1.73	63.66
Tmax (Median)	(h)	1.00	0.83	N/AP	3.00	3.00	N/AP

Following table represents food effect analysis of zolpidem treatments.

Table 13: Food Effect Assessment Summary (Sponsor's Analysis)

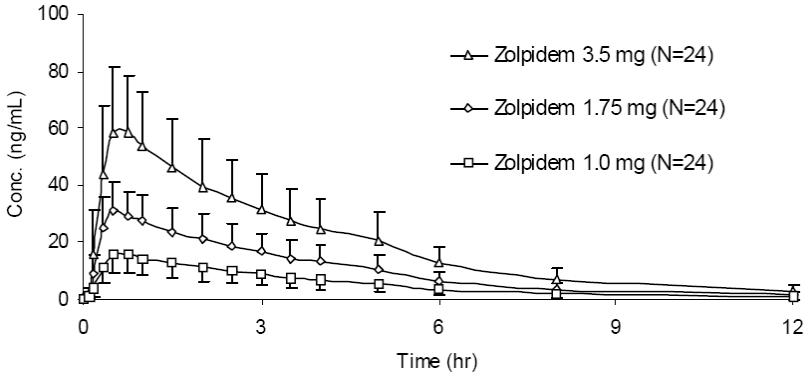
Treatment Comparisons	**Parameter**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**	**Intra-Subject CV%**
3.5 mg Intermezo® Fed/3.5 mg Intermezo® Fasting	AUC_{0-t}	81.04	76.12	86.27	15.27
	$AUC_{0-\infty}$	104.03	95.37	113.49	20.76
	C_{max}	57.77	51.1	65.32	30.47

Are Intermezzo® sublingual tablet formulations dose proportional?

Dose-proportionality of the zolpidem plasma concentrations resulting from the administration of the sublingual tablet 1, 1.75 and 3.5 mg was determined in Study ZI-05-009 (using IND formulation which is bioequivalent to to-be-marketed formulation). The results indicated that the sublingual tablet formulation was dose-proportional with respect to zolpidem PK parameters. Dose proportionality was also assessed with proposed commercial formulation in elderly cohort with 1.75 and 3.5 mg sublingual tablet (see table 14).

Following figure represents the mean (SD) plasma concentration-time profiles of sublingual zolpidem in the 1.0, 1.75, and 3.5 mg treatment groups.

Figure 2: Mean (SD) Zolpidem plasma concentration-time profiles after administration of zolpidem 3.5, 1.75 and 1.0 mg.



A summary of the statistical analyses of zolpidem PK parameters after administration of sublingual zolpidem 3.5, 1.75 and 1.0 mg are presented in the following table:

Table 15: Statistical Analysis (ANOVA) of Zolpidem Plasma Pharmacokinetic Parameters After Administration of Zolpidem 1.0, 1.75 and 3.5 mg

		Test/Reference Geometric Mean Ratio (%) (90% confidence interval) (N=24)		
Test	**Reference**	**Cmax**	**AUC0-t**	**AUC0- inf**
Zolpidem 1.0 mg	Zolpidem 1.75 mg	90.22 (79.69-102.14%)	88.23 (74.92-103.89%)	88.51 (75.15-104.25%)
Zolpidem 1.0 mg	Zolpidem 3.5 mg	90.90 (80.29-102.91%)	90.79 (77.10-106.91%)	90.98 (77.24-107.16%)
Zolpidem 1.75 mg	Zolpidem 3.5 mg	100.75 (88.99-114.06%)	102.91 (87.39-121.18%)	102.79 (87.27-121.07%)

Does this application support lower dose (1.75 mg) zolpidem tartrate sublingual tablet for the geriatric and debilitated populations?

Yes. This application provides PK data in geriatric population after administration of 1.75 mg and 3.5 mg Intermezzo® sublingual tablet. The mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher in elderly subjects compared to Adults.

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative-hypnotic drugs and the difference (higher) in the exposure to zolpidem is a concern in the treatment of elderly. Therefore the recommended dose in elderly is half the adult dose (1.75 mg) similar to other zolpidem products including the reference Ambien®.

Is there an early onset of absorption from sublingual (Intermezzo®) tablet when compared to reference Ambien®?

Yes, partial area under the curve upto the time to reach maximum concentration ($AUC_{0\text{-}tmax}$) indicate that there is an early onset of absorption from sublingual tablet when compared to Ambien®. The $AUC_{0\text{-}tmax}$ was 39% greater for Intermezzo® treatment when compared to reference Ambien®.

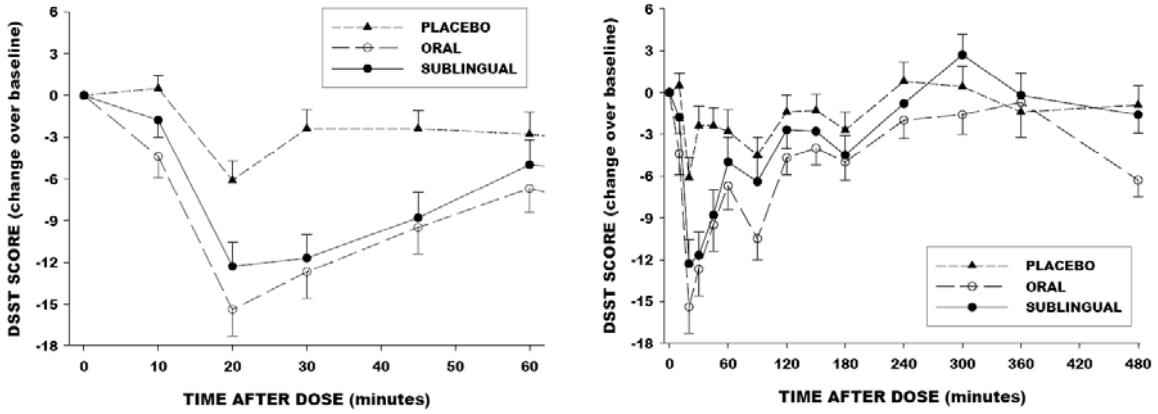
$AUC_{0\text{-}tmax}$ was calculated from the individual subject plasma concentration time data provided for the test, Intermezzo® (3.5 mg, sublingual zolpidem tartrate tablet) and the reference Ambien® (10 mg, oral zolpidem tartrate tablet) in the Study ZI-15. According to the statistical analysis, ANOVA detected a statistically significant difference between treatments for $AUC_{0\text{-}tmax}$. The ratio of partial area under the concentration time curve was 139 and the lower and upper 90% confidence interval (CI) limits are 103.1 and 187.2 respectively for dose normalized Intermezzo® treatment when compared to reference Ambien® under fasting conditions as shown in the table below.

Table 16: Treatment comparisons using ANOVA: 3.5 mg Sublingual Zolpidem Tartrate Tablet and 10 mg Oral Ambien® Under Fasted Conditions

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
3.5 mg Intermezzo® Fasting/10 mg Ambien® Fasting	$AUC_{0\text{-}tmax}$	138.9	103.1	187.2

However, DSST change from baseline was similar or greater for oral tablets as shown in the figure below.

Mean (±SE, n=35) changes over baseline in DSST score. left: 0-61 minutes; right: 0-481 minutes.



Based on the concentration time profile after a single dose of 3.5 mg sublingual tablet

a) **How long does it take to lose 90% of maximum concentration attained?**
b) **What percentage of maximum plasma concentration (Cmax) remaining at 3 and 4 hrs?**

Maximum plasma concentration (Cmax) attained after a single dose administration of 3.5 mg zolpidem sublingual tablet was approximately 47 ng/mL. At approximately 6 hrs and 33 minutes, plasma concentration of zolpidem would be 10% of Cmax.

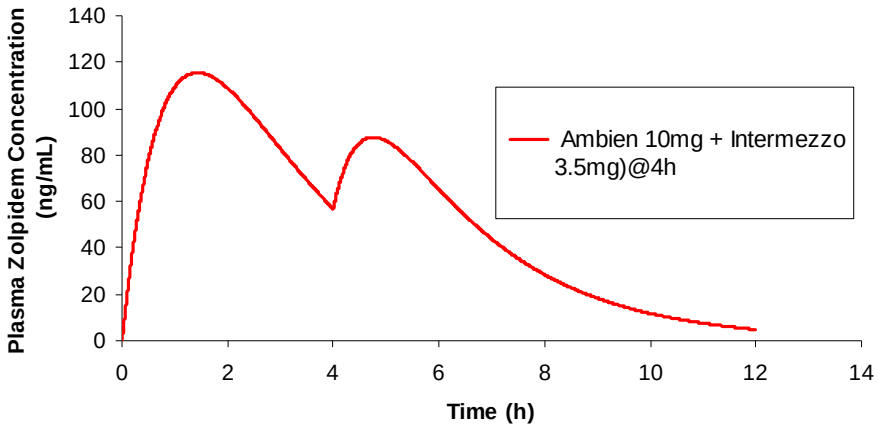
Zolpidem plasma concentration after 3 and 4 hrs would be approximately 25.6 ng/mL or 54% of Cmax and 16.1 ng/mL or 34% of Cmax respectively.

What are the predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of zolpidem (as 3.5 mg sublingual tablet) following first 10 mg dose (Ambien®) separated by 4 hrs.

The predicted zolpidem concentrations at 2, 4 and 6 hrs were 65.2, 28.5 and 11.7 ng/mL respectively.

Individual plasma concentrations were obtained from Study ZI-15 to calculate primary PK parameters for 10 mg Ambien® and 3.5 mg sublingual zolpidem tablet. These parameters were used simulate plasma concentrations at different time points as shown in the figure below.

Predicted zolpidem plasma concentration time profile

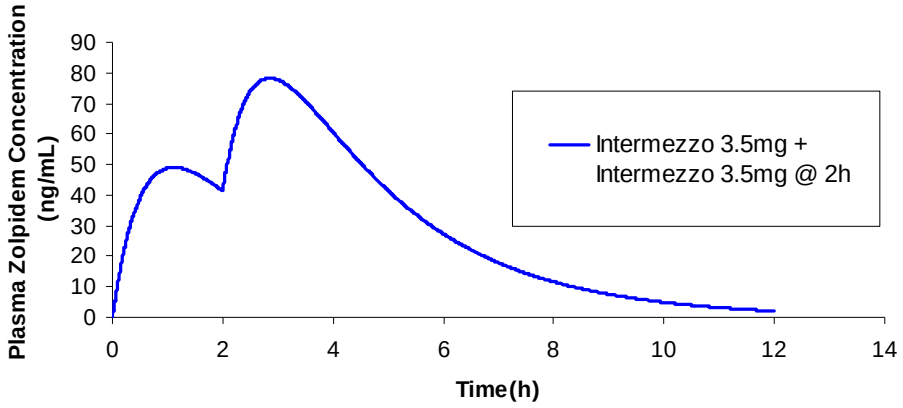


What are the predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of 3.5 mg sublingual tablet following first 3.5 mg dose separated by 2 hrs.

The predicted zolpidem concentrations at 2, 4 and 6 hrs were 60.4, 27.3 and 11.6 ng/mL respectively.

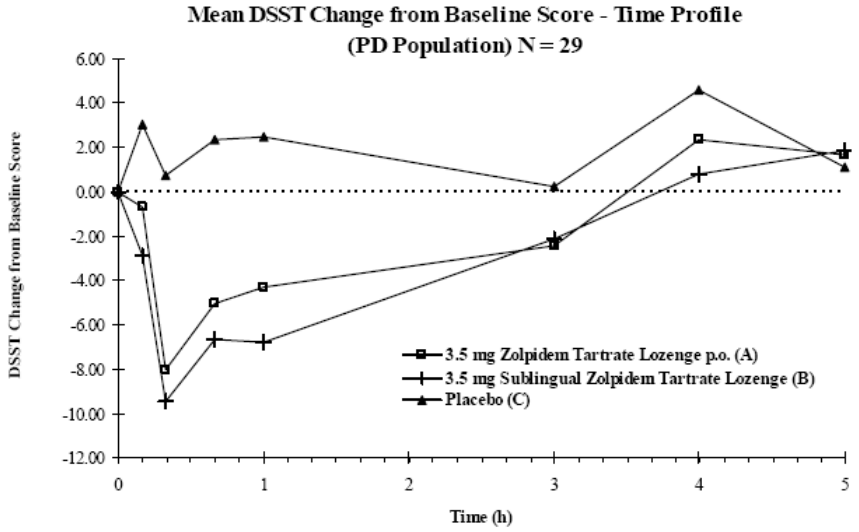
Individual plasma concentrations were obtained from Study ZI-15 to calculate primary PK parameters for 3.5 mg sublingual zolpidem tablet. These parameters were used simulate plasma concentrations at different time points as shown in the figure below.

Predicted zolpidem plasma concentration time profile



What is the difference between pharmacodynamic effects in patients when compared to placebo in case of potential re-dosing of Intermezzo less than 4 hours remaining to sleep.

In a pharmacodynamic study ZI-16 with Intermezzo DSST scores were evaluated for sublingual and oral (immediate swallowing) administration in comparison with placebo treatment. Pharmacokinetic samples were also taken at 0, 1, 2, 3, and 5 hours. DSST scores returned to the baseline within 3- 4 hrs postdose corresponding to 30 ng/mL approximate mean plasma zolpidem concentration.



Predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of 3.5 mg sublingual tablet following first 3.5 mg dose separated by 2 hrs were 60.4, 27.3 and 11.6 ng/mL respectively.

Predicted zolpidem concentraions at 2, 4 and 6 hrs after a second dose of 3.5 mg sublingual tablet following first 10 mg dose (Ambien®) separated by 4 hrs were 65.2, 28.5 and 11.7 ng/mL respectively

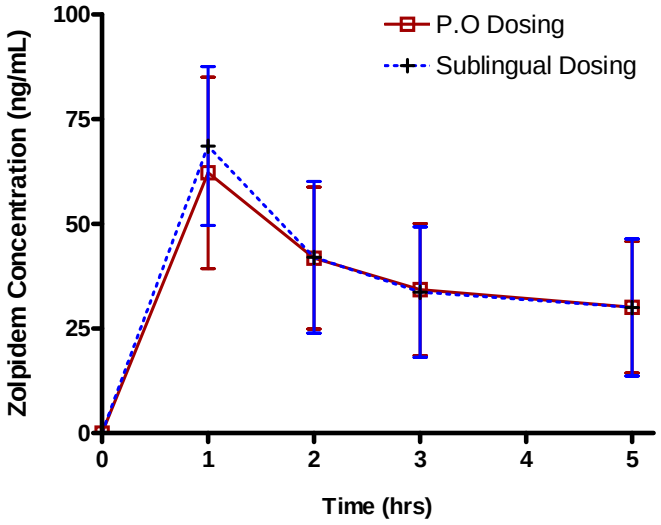
Pharmacodynamic effects may be comparable to that of placebo at after 4 hours of second dose in these cases of potential re-dosing.

Is there a difference in PK profile for sublingual (Intermezzo®) tablet after immediate swallowing when compared to sublingual administration?

The sponsor has conducted a pharmacodynamic study comparing the difference in digital symbol substitution test (DSST) and electroencephalogram (EEG) between sublingual administration and immediate swallowing of sublingual tablet with placebo. In this study five PK samples per subject were obtained to characterize plasma concentration time profile.

Following figure represents PK profiles for both treatments of zolpidem formulations (sublingual and p.o dosing).

Mean (SD) plasma zolpidem concentrations time profile obtained after sublingual and p.o dosing.



PK sampling time points were inadequate to quantitate the absorption differences between sublingual and oral administration. However, Pharmacokinetic profile appears to be similar for both sublingual and immediate swallowing (p.o dosing).

Is there a pharmacodynamic evidence of effectiveness of Intermezzo® for the indication?

This NDA included three pharmacodynamic studies (ZI-05-009, ZI-16 and ZI-17) to evaluate hypnotic effects of sublingual zolpidem tablet. Study ZI-05-009 compared DSST scores obtained after administration of three different doses (1, 1.75 and 3.5 mg) of sublingual zolpidem tablets with the placebo. Study ZI-16 compared pharmacodynamic effects of sublingual tablet formulation with placebo and same formulation after immediate swallowing (p.o dosing). Study ZI-17 compared hypnotic effects of sublingual zolpidem with placebo and 3.5 mg oral zolpidem tartrate tablet formulated specifically for this study. (b) (4)

Compared to placebo, sublingual zolpidem significantly decreased Digit Symbol Substitution Test (DSST), Visual Analogue Scale (VAS), Choice Reaction Time (CRT). There was no statistically significant difference for pharmacodynamic endpoints for sublingual zolpidem treatment when compared to oral zolpidem tablet (ZI-17) or sublingual zolpidem formulation given orally (p.o, ZI-16).

The adequacy of the labeling recommendations of these studies should also be considered by the medical officer.

E. Analytical

Have the analytical methods been sufficiently validated?

Yes (both pre-study validation and within study performance).

Method: The analyte zolpidem and its internal standard (b) (4) were extracted from a 0.100 mL aliquot of human EDTA plasma into methyl-ter-butyl ether (MTBE) using a (b) (4) The extracted samples were injected into a liquid chromatography system equipped with a reverse phase C18 column. The mobile phase was a mixture of Milli-Q type water and methanol (40/60) with ammonium acetate 1 mM. The detection method used was tandem mass spectrometry.

Pre-Study Bioanalytical Method Validation

Analyte	Zolpidem
Internal standard (IS)	(b) (4)

Method description	HPLC-Reverse phase liquid chromatography with MS/MS detection
Limit of quantitation	1 ng/mL
Average recovery of drug (%)	83.95%
Average recovery of IS (%)	91.04%
Standard curve concentration range (ng/mL)	1-252 ng/mL
Potentially Interfering Drugs:	No effect on analyte quantitation
Freeze and Thaw Stability Precision at -80ºC:	QC coefficients of variation: 1.61 and 0.76%
Short-Term Stability of Analyte in Matrix at Room Temperature:	Mean % change after 11 hours: 5.22 and -2.85%
Long-Term Stability of Analyte in Matrix at -20ºC:	Mean % change after 72 days: 6.09 and -4.36%
Long-Term Stability of Analyte in Matrix at -80ºC:	Mean % change after 57 days: 2.15 and 3.92%
Long-Term Stability of Analyte in Solution at -20ºC:	Mean % change after 55 days: -2.14%
Long-Term Stability of Analyte in Solution at -80ºC:	Mean % change after 55 days: -3.75%
Long-Terrn Stability of Internal Standard in Solution at -20ºC:	Mean % change after 55 days: -1.67%
Long-Terrn Stability of Internal Standard in Solution at -80ºC:	Mean % change after 55 days: 3.26%

Partial validation was performed to support following changes:

1. Change in calibration range from 0.25 -62.5 ng/mL to 1- 252 ng/mL
2. To include hemolysis effect and matrix effect

Partial Validation 1

Linearity:	r > 0.9972
Calibration Curve Range:	1.01 to 252.40 ng/mL
Between-Run Accuracy:	QC % nominal concentrations: 97.55 to 105.25%

Between-Run Precision:	QC coefficients of variation: 2.83 to 4.43%
Recovery of Analyte:	QC means: 79.51, 75.80 and 75.34%
Recovery of Internal Standard:	Mean: 87.46%
Potentially Interfering Drugs:	No effect on analyte quantitation
Matrix Effect:	No effect on analyte quantitation
Hemolysis Effect Accuracy:	QC % nominal concentrations: 101.79 and 92.74%
Hemolysis Effect Precision	QC coefficients of variation: 1.36 and 1.36%
Reinjection Reproducibility Accuracy after 52 Hours at Room Temperature:	QC % nominal concentrations after 52 Hours: 91.58 to 103.84%
Reinjection Reproducibility Precision after 52 Hours at Room Ternperature:	QC coefficients of variation: 2.20 to 2.93%
Sample Collection and Handling stability at 4ºC	Mean % change after 291 minutes: -1.58%
Adsorption of Analyte onto Collection Devices:	Mean % change: 0.20%
Short-Term Stability of Analyte in Solution at Room Temperature:	Mean % change after 6 hours: 2.94%
Short-Term Stability of Internal Standard in Solution at Room Temperature:	Mean % change after 6 hours: 9.14%

Partial Validation 2

Linearity:	$R^2 > 0.9964$
Calibration Curve Range:	0.25 to 62.50 ng/mL
Between-Run Accuracy:	QC % nominal concentrations: 99.33 to 104.87%
Between-Run Precision:	QC coefficients of variation: 5.43 to 8.55%
Within-Run Accuracy:	QC % nominal concentrations: 95.56 to 104.00%
Within-Run Precision:	QC coefficients of variation: 2.68 to 6.40%
Matrix Selectivity:	No significant interference observed in tested matrices for zolpidem and internal standard

Potentially Interfering Drugs;	No effect on analyte quantitation
Lower Limit of Quantitation (LLOQ):	0.25 ng/mL with a signal to noise ratio of 144
Hemolysis Effect Accuracy:	QC % nominal concentrations: 108.34 and 108.31%
Hemolysis Effect Precision:	QC coefficients of variation: 5.71 and 4.03%

III. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Intermezzo® and finds it acceptable pending the following revision:

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

26 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

IV. APPENDIX

A Individual Study Synopsis

ZI-13: A randomized, open-label, two-period, two-sequence crossover study to evaluate the bioequivalence of two different formulations of sublingual zolpidem tartrate tablet in healthy adult subjects

Objectives:

Primary:
The primary objective of this study was to evaluate the bioequivalence of the proposed commercial formulation of 3.5 mg sublingual zolpidem tartrate tablets (Test material or Treatment A) against the IND formulation of 3.5 mg sublingual zolpidem tartrate tablets (Reference material or Treatment B) following single sublingual doses to healthy, adult subjects.

Secondary:
The secondary objectives were to further characterize the safety and tolerability of 3.5 mg sublingual zolpidem tartrate tablets following single sublingual doses in healthy, adult subjects.

Study Design	Single-centre, open, single-dose, randomized, two-period crossover trial	
Study Population	Healthy male and female Age: 18-55 years BMI: 18.0- 34.0 kg/m^2 36 subjects (23 females and 13 males) were randomized, and 32 completed the study	
Treatment Groups	Treatment A = 3.5 mg sublingual zolpidem tartrate tablet (proposed commercial formulation) Treatment B = 3.5 mg sublingual zolpidem tartrate tablet (IND formulation) The treatment phases were separated by washout periods of 7±2 days.	
Treatment Instructions	The subjects were instructed to place the drug tablet under the tongue and hold it there as it dissolved. While the tablet was dissolving, the subjects were instructed to avoid swallowing for the first 2 minutes after the drug was placed under the tongue and to move the tablet with the tongue to help it dissolve more quickly.	
Dosage and Administration	**Reference: IND Formulation** - 3.5 mg sublingual zolpidem tartrate tablet (IND formulation) - single dose, under fasting condition	**Test: Commercial Formulation** - 3.5 mg sublingual zolpidem tartrate tablet (proposed commercial

<table>
<tr><td></td><td></td><td>formulation)
- single dose, under fasting condition</td></tr>
<tr><td>Sampling: Blood</td><td colspan="2">Blood samples were collected prior to study drug administration (within 1 hour pre-dose) and at 5, 10, 15, 20, 25, 30, 40, and 50 minutes post-dose, and 1, 1.5, 2, 3, 4, 5, 6, and 8 hours post-dose in each period.</td></tr>
<tr><td>Analysis</td><td colspan="2">Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantitation of 0.25 ng/mL.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>0.75, 9.38, 18.75 and 43.75 ng/mL</td><td>0.25, 0.5, 2.5, 12.5, 25, 50, and 62.5 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.6 to 14.99</td><td>2.2 to 4.0</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.998</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">0.25 to 62.5 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">0.25 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td colspan="2">None</td></tr>
<tr><td>Feces</td><td colspan="2">None</td></tr>
<tr><td>PK Assessments</td><td colspan="2">Primary: (AUC_{0-t}, AUC_{0-inf} and C_{max});
Secondary: ($AUC_{t/inf}$, T_{max}, $T_{1/2\ el}$, and K_{el})</td></tr>
<tr><td>PD Assessments</td><td colspan="2">None</td></tr>
<tr><td>Statistical Methods</td><td colspan="2">Pharmacokinetics:
• Parametric ANOVA on AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2\ el}$ and K_{el}; geometric confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max};
• Covariates in the ANOVA model: sequence, subject within sequence, period and treatment;
• Ln-transformed parameters: AUC_{0-t}, AUC_{0-inf} and C_{max}.

Criteria for Bioequivalence for zolpidem tartrate :
90% geometric confidence interval of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf and Cmax should be within 80.00% to 125.00%.</td></tr>
</table>

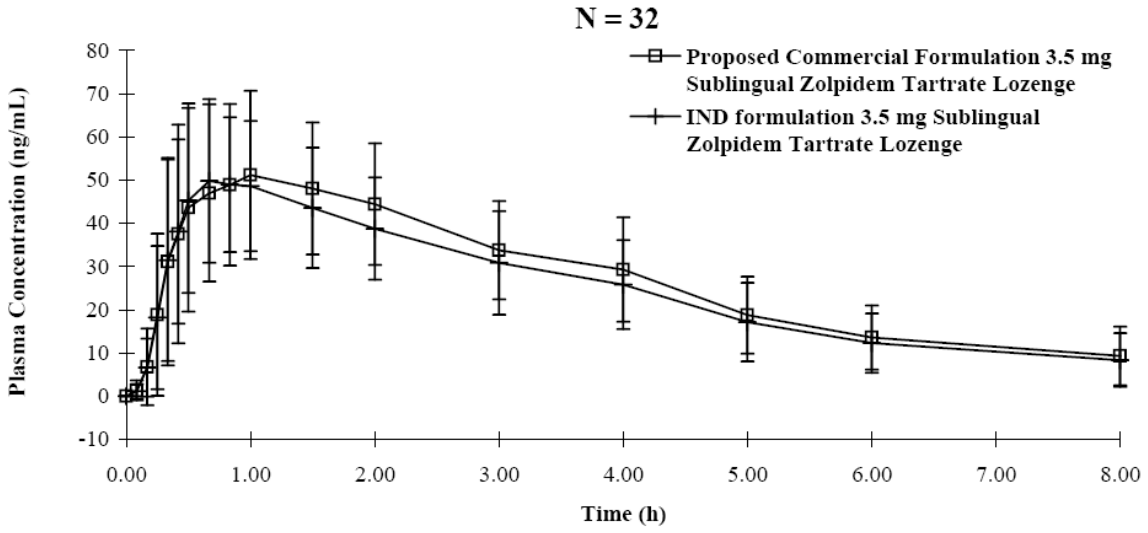
RESULTS:

Bioequivalence: Bioequivalence criteria was met between commercial formulation and IND formulation under fasting conditions. The geometric mean ratio of commercial

formulation and IND formulation for the $AUC_{0-\infty}$ was 109.2 with 90% CI = (103.3, 115.3). Cmax geometric mean ratio was 102.9 with 90% CI = (93.9, 112.8).

The mean zolpidem plasma concentration (±SD) vs time profiles are presented by treatment formulation in the figure below.

Figure 3: Mean zolpidem (± SD) plasma concentrations (ng/mL) vs time profiles



Following table lists PK parameters calculated for different treatments.

Table 17: Summary of Pharmacokinetic Results-Zolpidem (N = 32)

Parameters		**Proposed commercial formulation 3.5 mg sublingual zolpidem tartrate tablet (A)**			**IND formulation 3.5 mg sublingual zolpidem tartrate tablet (B)**		
		Mean	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	215.51	74.63	34.63	197.74	70.83	35.82
AUC0-inf	(ng·h/mL)	253.56	113.51	44.77	233.74	111.44	47.68
AUCt/inf	(%)	87.70	7.33	8.36	87.88	7.98	9.08
Cmax	(ng/mL)	62.93	21.51	34.17	60.44	19.04	31.50
Tmax	(h)	0.933	0.436	46.77	0.742	0.396	53.38
Tmax *	(h)	0.858	0.500	-	0.667	0.333	-
Kel	(h-1)	0.3201	0.0952	29.73	0.3162	0.0871	27.55

T½ el	(h)	2.36	0.73	30.85	2.40	0.88	36.62

* Medians and interquartile ranges are presented.

Bioequivalence analysis of zolpidem treatments

Following table represents bioequivalence analysis of proposed commercial formulation and IND formulation.

Table 18: Bioequivalence Analyis: Proposed Commercial Formulation 3.5 mg Sublingual Zolpidem Tartrate Tablet (A) vs IND Formulation 3.5 mg Sublingual Zolpidem Tartrate tablet (B) (Sponsor's Analysis)

Treatment Comparisons	**Parameter**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**	**Intra-Subject CV**
Commercial Formulation / IND Formulation	AUC_{0-t}	109.0	103.4	115.1	12.7%
	$AUC_{0-\infty}$	109.2	103.3	115.3	13.0%
	C_{max}	102.9	93.9	112.8	21.8%

Reviewer's re-analysis of the data showed similar 90% confidence interval (CI) limits for AUC and Cmax as shown in the table below.

Table 19: Analysis of Bioequivalence Between Proposed Commercial Formulation (3.5 mg Sublingual Zolpidem Tartrate Tablet, A) vs IND Formulation (3.5 mg Sublingual Zolpidem Tartrate tablet, B) (Reviewer's Analysis)

Treatment Comparisons	**Parameter**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**
Commercial Formulation / IND Formulation	$AUC_{0-\infty}$	109.1	103.3	115.3
	C_{max}	102.9	93.95	112.8

90% geometric confidence intervals of the ratio of least-squares means of the test to reference product of ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptance range of 80% to 125%. Time to reach maximum concentration (Tmax) was not statistically significantly different between IND formulation and commercial formulation.

Conclusions

- The proposed commercial formulation (3.5 mg strength) of sublingual zolpidem tartrate tablet (Treatment A) is bioequivalent to the IND formulation (3.5 mg strength) of sublingual zolpidem tartrate tablet (Treatment B).
- Time to reach maximum concentration (Tmax) was not statistically significantly different between IND formulation and commercial formulation

ZI-15: A study to assess the comparative single-dose pharmacokinetics of 3.5 mg sublingual zolpidem tartrate tablets (Intermezzo®) in the fed and fasted state, and 10 mg oral zolpidem tartrate (Ambien®) in the fasted state in healthy adult subjects

Objectives:

Primary objectives

1. Comparison between the AUC0-inf, AUC0-t and Cmax under fed and fasted states for 3.5 mg sublingual zolpidem tartrate tablet
2. Comparison between AUC0-inf, AUC0-t, and Cmax under fasted conditions for 3.5 mg sublingual zolpidem tartrate tablet vs. 10 mg oral zolpidem tartrate tablet

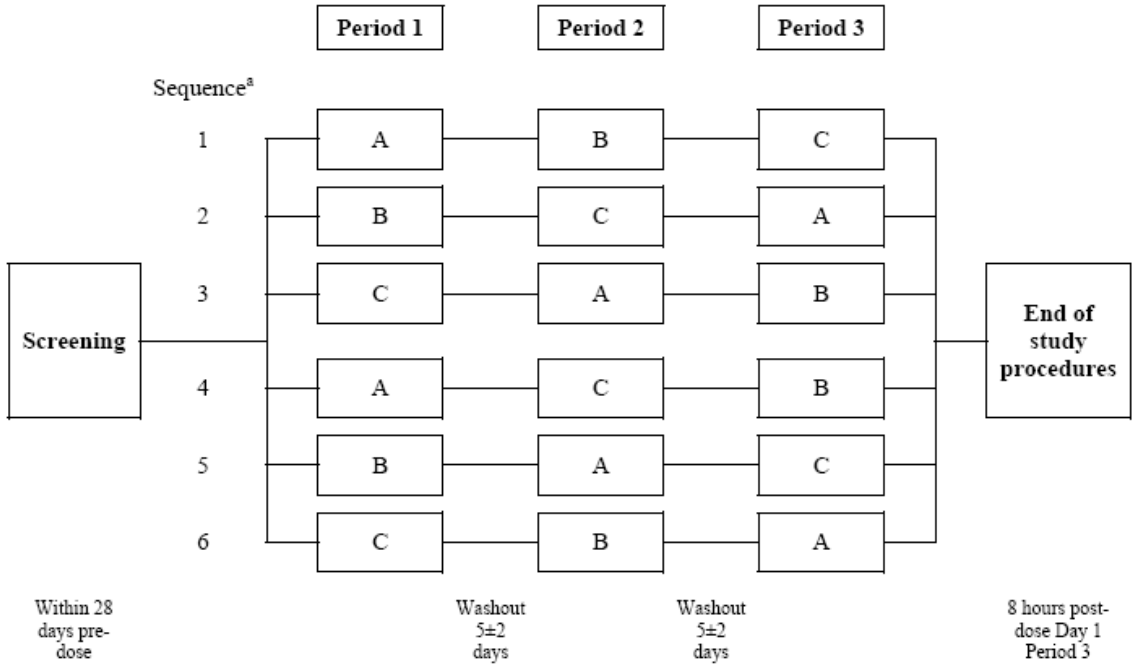
Study Design	Single-centre, open, single-dose, randomized, three-period crossover trial	
Study Population	Healthy male and female Age: 18-64 years BMI: 18.0- 32.0 kg/m^2 36 subjects were randomized, and 33 completed the study	
Treatment Groups	Treatment A = 3.5 mg sublingual zolpidem tartrate tablet under fasted conditions Treatment B = 3.5 mg sublingual zolpidem tartrate tablet under fed conditions Treatment C = 10 mg oral zolpidem tartrate tablet under fasted conditions The treatment phases were separated by washout periods of 5±2 days.	
Treatment Instructions	The subjects were instructed to place the drug tablet under the tongue and hold it there as it dissolved. While the tablet was dissolving, the subjects were instructed to avoid swallowing for the first 2 minutes after the drug was placed under the tongue and to move the tablet with the tongue to help it dissolve more quickly. The reference medication (Treatment C) was swallowed immediately with 240 mL of water.	
Dosage and Administration	**Reference: Ambien** - 10 mg, oral tablet - single dose, under fasting condition	**Test: Sublingual Tablet** - 3.5 mg, sublingual tablet - single dose, under fasting or fed condition

<table>
<tr><td>Sampling: Blood</td><td>Blood samples were collected prior to study drug administration (within 1 hour (h) pre-dose) and at 5, 10, 15, 20, 25, 30, 40, and 50 minutes (min) post-dose, and 1, 1.5, 2, 3, 4, 5, 6, and 8 h post-dose in each period.</td></tr>
<tr><td>Analysis</td><td>Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantitation of 1 ng/mL.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>3.0, 25, 75, and 175 ng/mL</td><td>1, 2, 5, 50, 100, 200, and 250 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.15 to 5.48</td><td>2.71 to 4.76</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.998</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">1 to 250ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td>None</td></tr>
<tr><td>Feces</td><td>None</td></tr>
<tr><td>PK Assessments</td><td>Primary: (AUC_{0-t}, AUC_{0-inf} and C_{max});
Secondary: ($AUC_{t/inf}$, AUC_{0-4h}, $AUC_{0-[25\ ng/mL]}$, $T_{[25\ ng/mL]}$, $T_{½max}$, T_{max}, $T_{1/2\ el}$, and K_{el})
Additional parameters: AUC_{0-1h}, $AUC_{0-[Tmax]}$, $AUC_{0-15\ min}$, $AUC_{0-20\ min}$, $C_{15\ min}$, and $C_{20\ min}$</td></tr>
<tr><td>PD Assessments</td><td>None</td></tr>
<tr><td>Statistical Methods</td><td>Pharmacokinetics:
Parametric ANOVA on AUC_{0-t}, AUC_{0-inf}, C_{max}, AUC_{0-4h}, $AUC_{0-[25\ ng/mL]}$, $T_{[25\ ng/mL]}$, $T_{½max}$, T_{max}, $T_{1/2\ el}$, and K_{el}, as well as for additional parameters AUC_{0-1h}, $AUC_{0-[Tmax]}$, $AUC_{0-15\ min}$, $AUC_{0-20\ min}$, $C_{15\ min}$, and $C_{20\ min}$; geometric confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max};
Covariates in the ANOVA model: group, sequence, sequence*group, subject within sequence*group, period within group, treatment and treatment*group;
Ln-transformed parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, AUC_{0-4h}, $AUC_{0-[25\ ng/mL]}$, AUC_{0-1h}, $AUC_{0-[Tmax]}$, $AUC_{0-15\ min}$, $AUC_{0-20\ min}$, $C_{15\ min}$, and $C_{20\ min}$.
<u>Food Effect:</u> No food effect was to be concluded for sublingual zolpidem tartrate tablet 3.5 mg if the 90% geometric confidence interval of the ratio (B/A) of least-squares means from the ANOVA of the ln transformed AUC0-t, AUC0-inf and Cmax was within</td></tr>
</table>

	80.00% to 125.00%. <u>Comparison to Oral Ambien® 10 mg:</u> If the upper boundary of the 90% confidence intervals of the ratio (A/C) of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} was less than 125.00%, then the results indicated that the rate and extent of exposure to zolpidem from the 3.5 mg sublingual zolpidem tartrate tablets fell at or below the currently marketed reference drug, 10 mg oral zolpidem tartrate tablets (Ambien®).

Following figure represents the study design adopted for this study

Figure 1: Study Design



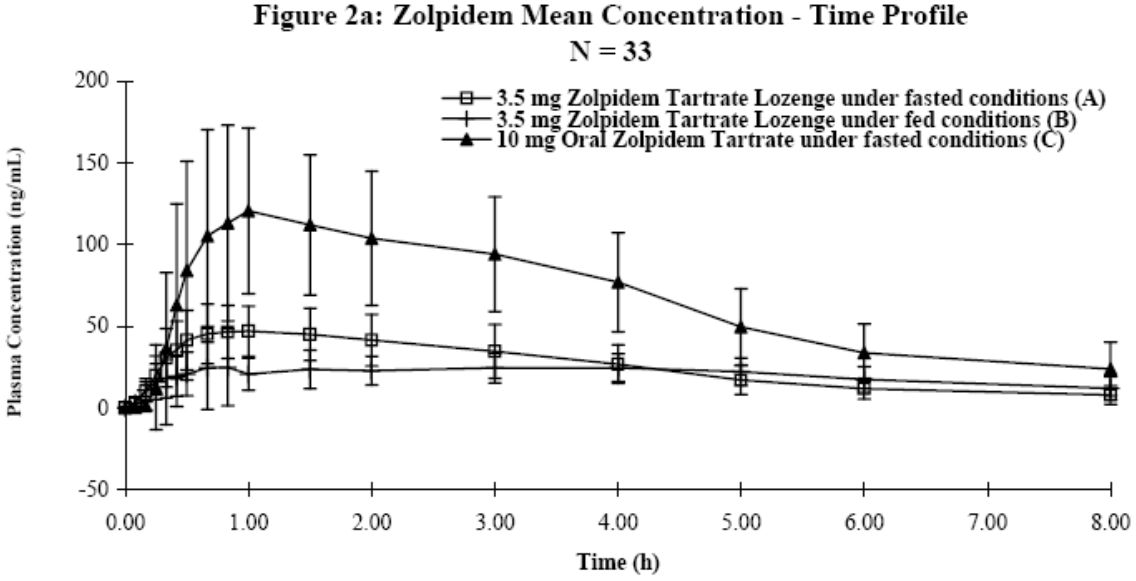
RESULTS:

<u>Relative Bioavailability</u>: This study was conducted to compare relative bioavailability between final commercial formulation and the reference Ambien®.

Comparison of pharmacokinetic parameters (AUC0-inf, AUC0-t and Cmax) under fasted conditions for 3.5 mg sublingual zolpidem tartrate tablet vs. 10 mg oral zolpidem tartrate (Ambien®) tablet indicate that the systemic exposure ($AUC_{0\text{-}inf}$ and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate tablet is well within the exposure of a 10 mg oral zolpidem tartrate tablet (Ambien®).

The geometric mean zolpidem plasma concentration (±SD) vs time profiles are presented by treatment in the figure below.

Figure 4: Mean zolpidem (± SD) plasma concentrations (ng/mL) vs time profiles



Following table indicates the PK parameters for different treatments.

Table 20: Summary of Pharmacokinetic Results – 3.5 mg Sublingual Zolpidem Tartrate Tablet (N = 33) and 10 mg Oral Ambien® Under Fasted Conditions

		3.5 mg Sublingual Zolpidem Tartrate Tablet under Fasted			10 mg Oral Zolpidem Tartrate Tablet (Ambien®) under Fasted		
Parameters	**Units**	**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	201.40	74.29	36.89	525.29	188.09	35.81
AUC0-inf	(ng·h/mL)	231.41	100.06	43.24	620.71	281.80	45.40
AUC0-4h	(ng·h/mL)	145.48	48.36	33.24	362.85	124.59	34.34
AUCt/inf	(%)	89.10	6.16	6.92	87.31	7.50	8.59
AUC0-15 min	(ng·h/mL)	1.91	1.04	54.57	0.64	1.28	200.37
AUC0-20 min	(ng·h/mL)	3.97	2.02	50.80	2.68	4.18	156.25
AUC0-[25 ng/mL]	(ng·h/mL)	6.82	7.32	107.34	7.48	14.75	197.28
AUC0-1h	(ng·h/mL)	32.59	12.22	37.51	67.32	38.58	57.31
AUC0-[Tmax]	(ng·h/mL)	41.61	42.05	101.05	73.26	69.44	94.79
C15 min	(ng/mL)	19.85	11.88	59.88	12.49	25.96	207.82
C20 min	(ng/mL)	30.48	17.94	58.86	36.11	46.49	128.77
Cmax	(ng/mL)	57.18	15.88	27.76	146.60	50.91	34.73

Tmax (Mean)	(h)	1.21	0.85	70.02	1.18	0.86	73.25
Tmax (Median)	(h)	1.00	0.83	N/AP	0.833	0.600	N/AP
T1/2max	(h)	0.450	0.434	96.45	0.583	0.418	71.64
T[25 ng/mL]	(h)	0.516	0.509	98.70	0.562	0.512	91.16
Kel	(h^{-1})	0.3327	0.0873	26.24	0.3204	0.0826	25.77
T½ el	(h)	2.23	0.61	27.13	2.33	0.74	31.77

Treatment A (3.5 mg sublingual zolpidem tartrate tablet under fasted conditions)
Treatment C (10 mg oral zolpidem tartrate tablet (Ambien®) under fasted conditions)

Mean values (% CV) for AUC_{0-t} were 201.40 ng · h/mL (36.89%) for Treatment A and 525.29 ng · h/mL (35.81%) for Treatment C. Mean values (% CV) for AUC_{0-inf} were 231.41 ng · h/mL (43.24%) for Treatment A and 620.71 ng · h/mL (45.40%) for Treatment C. Mean values (% CV) for C_{max} were 57.18 ng/mL (27.76%) for Treatment A and 146.60 ng/mL (34.73%) for Treatment C.

The apparent half-life was calculated for each subject and treatment. Mean values (% CV) for the $T_{1/2\ el}$ were 2.23 h (27.13%) for Treatment A and 2.33 h (31.77%) for Treatment C.

Area under the concentration-time curve from time 0 to 4h (AUC_{0-4h}) was calculated for each subject and treatment. Mean values (% CV) for AUC_{0-4h} were 145.48 ng·h/mL (33.24%) for Treatment A and 362.85 ng·h/mL (34.34%) for Treatment C.

Area under the concentration-time curve from time 0 to the first concentration above 25 ng/mL ($AUC_{0-[25\ ng/mL]}$) was calculated for each subject and treatment. Mean values (% CV) for $AUC_{0-[25\ ng/mL]}$ were 6.82 ng·h/mL (107.34%) for Treatment A and 7.48 ng·h/mL (197.28%) for Treatment C.

Relative bioavailability assessment of zolpidem treatments

Following table represents relative bioavailability assessment of zolpidem treatments.

Table 21: Relative Bioavailability Assessment of 3.5 mg Sublingual Zolpidem Tartrate Tablet and 10 mg Oral Ambien® Under Fasted Conditions (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
3.5 mg Intermezo® Fasting/10 mg	AUC_{0-t}	38.2	35.88	40.67
	$AUC_{0-\infty}$	37.8	34.72	41.15

Ambien® Fasting	C_{max}	39.28	34.73	44.43

According to the sponsor's analysis, ANOVA detected a statistically significant difference between treatments for $AUC_{0\text{-}inf}$ and Cmax.

The results indicate that the systemic exposure ($AUC_{0\text{-}inf}$ and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate lozenge is well within the exposure to zolpidem after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) which was found to be safe.

Food Effect – 3.5 mg Sublingual Zolpidem Tartrate Tablet under Fasted and Fed Conditions

Food effect on 3.5 mg sublingual zolpidem was also determined in this study. Refer to PK profile of treatment B in the above figure.

Consumption of a standard high-fat breakfast within 30 minutes of administration of the 3.5 mg sublingual zolpidem tartrate tablet showed a 20% decrease in the extent of systemic exposure ($AUC_{0\text{-}t}$) and did not affect area under the plasma concentration-time curve from time zero to infinity (extrapolated) ($AUC_{0\text{-}inf}$).

Following table indicates the PK parameters for different treatments.

Table 22: Summary of Pharmacokinetic Results – 3.5 mg Sublingual Zolpidem Tartrate Tablet Under Fasting and Fed Conditions

Parameters		**3.5 mg Sublingual Zolpidem Tartrate Tablet under Fasted**			**3.5 mg Sublingual Zolpidem Tartrate Tablet under Fed**		
		Mean	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	201.40	74.29	36.89	160.77	54.39	33.83
AUC0-inf	(ng·h/mL)	231.41	100.06	43.24	259.70	216.24	83.27
AUC0-4h	(ng·h/mL)	145.48	48.36	33.24	88.61	32.46	36.64
AUCt/inf	(%)	89.10	6.16	6.92	74.84	18.24	24.37
AUC0-15 min	(ng·h/mL)	1.91	1.04	54.57	1.82	1.13	61.72
AUC0-20 min	(ng·h/mL)	3.97	2.02	50.80	3.23	1.97	61.04
AUC0-[25 ng/mL]	(ng·h/mL)	6.82	7.32	107.34	27.12	31.06	114.51
AUC0-1h	(ng·h/mL)	32.59	12.22	37.51	17.99	11.44	63.62
AUC0-[Tmax]	(ng·h/mL)	41.61	42.05	101.05	53.32	37.51	70.35
C15 min	(ng/mL)	19.85	11.88	59.88	15.92	10.86	68.19
C20 min	(ng/mL)	30.48	17.94	58.86	18.00	11.77	65.41
Cmax	(ng/mL)	57.18	15.88	27.76	35.63	23.72	66.58

Tmax (Mean)	(h)	1.21	0.85	70.02	2.71	1.73	63.66
Tmax (Median)	(h)	1.00	0.83	N/AP	3.00	3.00	N/AP
T1/2max	(h)	0.450	0.434	96.45	0.601	0.653	108.68
T[25 ng/mL]	(h)	0.516	0.509	98.70	1.61	1.75	108.21
Kel	(h-1)	0.3327	0.0873	26.24	0.2496	0.1079	43.23
T½ el	(h)	2.23	0.61	27.13	4.05	4.39	108.34

Following table represents food effect analysis of zolpidem treatments.

Table 23: Food Effect Assessment Summary (Sponsor's Analysis)

Treatment Comparisons	**Parameter**	**Ratio**	**Lower 90% CI**	**Upper 90% CI**	**Intra-Subject CV%**
3.5 mg Intermezo® Fed/3.5 mg Intermezo® Fasting	AUC_{0-t}	81.04	76.12	86.27	15.27
	$AUC_{0-\infty}$	104.03	95.37	113.49	20.76
	C_{max}	57.77	51.1	65.32	30.47

The peak plasma concentration (C_{max}) decreased by approximately 38% and AUC0-t decreased by 19% on an average, following administration with food. Consumption of a standard high-fat breakfast within 30 minutes of administration of the 3.5 mg sublingual zolpidem tartrate tablet delayed time to reach the peak concentration (T_{max}) from 1 hour in the fasted state to ~3 hours in the fed state. Mean values (% CV) for the T_{max} were 1.21 h (70.02%) for Treatment A and 2.71 h (63.66%) for Treatment B.

The apparent half-life was calculated for each subject and treatment. The mean values (% CV) for the $T_{1/2\ el}$ were 2.23 h (27.13%) for Treatment A (3.5 mg sublingual zolpidem tartrate tablet, fasting) and 4.05 h (108.34%) for Treatment B (3.5 mg sublingual zolpidem tartrate tablet, fed).

Conclusions

Comparison of pharmacokinetic parameters (AUC0-inf, AUC0-t and Cmax) under fasted conditions for 3.5 mg sublingual zolpidem tartrate tablet vs. 10 mg oral zolpidem tartrate (Ambien®) tablet indicate that the systemic exposure (AUC_{0-inf} and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate lozenge is lower than the exposure after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) that was found to be safe.

- T_{max} values were statistically significantly different between the two treatments (Ambien® and sublingual zolpidem under fasting conditions).

- Food decreased the bioavailability of sublingual zolpidem and the time to reach the maximum concentration was delayed, similar to other zolpidem products.

ZI-14: A randomized, open-label, two period, two-sequence, crossover study to evaluate the pharmacokinetics (PK) of sublingual zolpidem tartrate tablet in healthy elderly subjects as compared to healthy non-elderly adult subjects

Objectives:

Primary:

- To evaluate the PK of zolpidem tartrate tablet 1.75 mg and 3.5 mg following single sublingual doses in healthy, elderly subjects.
- To evaluate the PK of zolpidem tartrate tablet 1.75 mg following single sublingual doses in healthy, elderly subjects compared to zolpidem tartrate tablet 3.5 mg in healthy, non-elderly subjects.

Secondary:

- To further characterize the safety and tolerability of the zolpidem tartrate tablets following single sublingual doses in healthy, elderly and adult non-elderly subjects.

Study Design	Single-centre, randomized, single-dose, open-label, 2-way crossover study	
Study Population	Elderly Cohort Age: >65years BMI: 18.0- 34.0 kg/m^2 24 subjects (16 females and 8 males) were randomized, and 23 completed the study Non-elderly Cohort Age: 18-55 years BMI: 18.0- 34.0 kg/m^2 24 subjects (9 females and 15 males) were randomized, and 24 completed the study	
Treatment Groups	Treatment A = 1.75 mg Sublingual Zolpidem Tartrate Tablet (to-be marketed formulation) Treatment B = 3.5 mg Sublingual Zolpidem Tartrate Tablet (to-be marketed formulation) The treatment phases were separated by washout periods of 5±2 days.	
Treatment Instructions	An oral cavity examination was performed prior to dosing, after which the subjects were then instructed to place the drug tablet under the tongue and hold it there while it dissolved. Saliva was swallowed every 2 minutes while the tablet was dissolving until the nearest 2 minutes after the tablet dissolved. An oral cavity examination was performed within 10 minutes after subjects signaled dissolution was completed.	
Dosage and	**Test:** Elderly subjects only as per	**Reference:** Elderly and

<table>
<tr><td>Administration</td><td>randomization
- 1.75 mg sublingual zolpidem tartrate tablet
- single dose, under fasting condition</td><td>non-elderly subjects as per randomization
- 3.5 mg sublingual zolpidem tartrate tablet
- single dose, under fasting condition</td></tr>
<tr><td>Sampling: Blood</td><td colspan="2">Blood samples were collected within 1 hour prior to drug administration; 5, 10, 15, 20, 25, 30, 40, and 50 minutes post-dose; and 1, 1.5, 2, 3, 4, 5, 8, and 12 hours post-dose in each period.</td></tr>
<tr><td>Analysis</td><td colspan="2">Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 1 ng/mL.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>3.0, 25, 75, and 175 ng/mL</td><td>1, 2, 5, 50, 100, 200, and 250 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>1.5 to 3.97</td><td>2.38 to 4.08</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.998</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">1 to 250 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td colspan="2">None</td></tr>
<tr><td>Feces</td><td colspan="2">None</td></tr>
<tr><td>PK Assessments</td><td colspan="2">Primary: (AUC_{0-t}, AUC_{0-inf} and C_{max});
Secondary: ($AUC_{t/inf}$, T_{max}, $T_{1/2\ el}$, and K_{el})</td></tr>
<tr><td>PD Assessments</td><td colspan="2">None</td></tr>
<tr><td>Statistical Methods</td><td colspan="2">Pharmacokinetics:
Cross-over design — elderly cohort (1.75 mg dose versus 3.5 mg dose)
• Parametric ANOVA on dose normalized (to 1.75 mg) AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, $AUC_{0-[25\ ng/mL]}$, and C_{max}; and geometric confidence intervals for AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, and C_{max};
• Non-parametric ANOVA on T_{max}, $T_{1/2\ el}$, K_{el}, $T_{½max}$, and $T_{[25\ ng/mL]}$;
• Covariates in the ANOVA model: sequence, subject within sequence, period, and treatment;
• Ln-transformed parameters on dose normalized (to 1.75 mg): AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, $AUC_{0-[25\ ng/mL]}$, and C_{max}.

Criteria for Bioavailability for zolpidem:</td></tr>
</table>

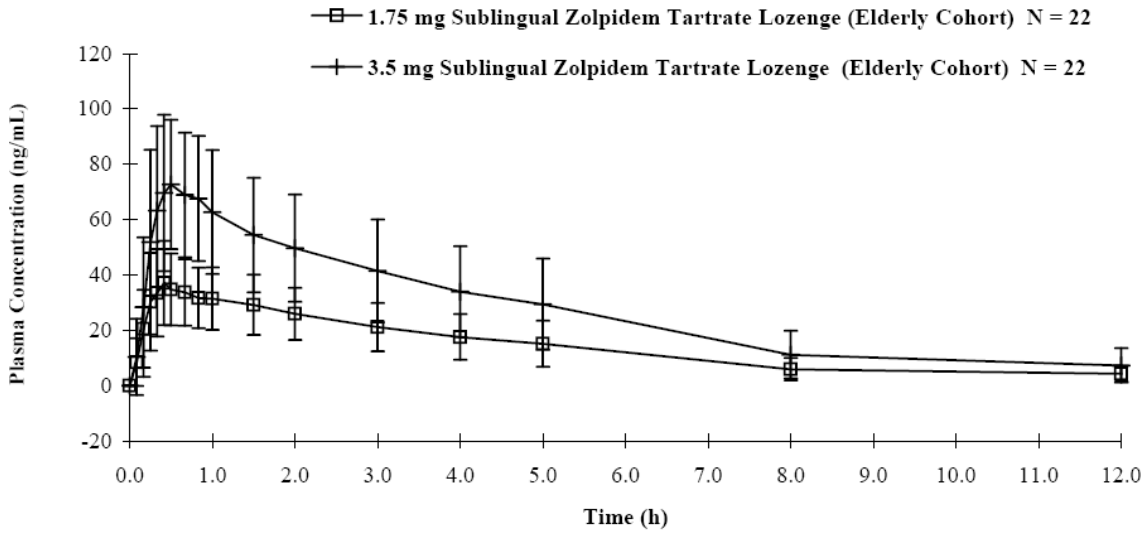
	• 90% confidence interval for the ratio (test/reference) should be completely within the range of 80 to 125% for AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, and C_{max}; the formulation should be deemed to have linear kinetics in healthy elderly subjects over the dose range studied. Parallel design — elderly cohort (1.75 mg dose) and adult non-elderly cohort (3.5 mg dose) • Parametric ANOVA on AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, C_{max}, T_{max}, $T_{1/2\ el}$ and K_{el}, $AUC_{0-[25\ ng/mL]}$, $T_{½max}$, and $T_{[25\ ng/mL]}$; and geometric confidence intervals for AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h}, and C_{max}; • Covariates in the ANOVA model: treatment (cohort); • Ln-transformed parameters: AUC_{0-t}, AUC_{0-inf}, AUC_{0-4h} , $AUC_{0-[25\ ng/mL]}$, and C_{max}. Criteria for Bioavailability for zolpidem: 90% confidence interval for the AUC0-t ratio (elderly 1.75 mg versus adult non-elderly 3.5 mg) should be within the range of 80 to 125% then the bioavailability of 1.75 mg in elderly subjects should be deemed similar to the bioavailability of 3.5 mg in adult non-elderly subjects.

RESULTS

Cross-over design — elderly cohort (1.75 mg dose versus 3.5 mg dose)

The mean zolpidem plasma concentration (±SD) vs time profiles are given in the figure below.

Figure 5: Mean zolpidem (± SD) plasma concentrations (ng/mL) vs time profiles



Following table represents PK parameters for different treatments.

Table 24: Summary of Pharmacokinetic Results of Zolpidem (N = 22)

		1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A)			3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B)		
Parameters		**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	164.71	75.05	45.56	320.08	151.78	47.42
AUC0-inf	(ng·h/mL)	181.41	89.83	49.51	352.45	187.94	53.32
AUC0-4h	(ng·h/mL)	100.57	36.91	36.70	194.15	72.46	37.32
AUCt/inf	(%)	92.20	4.49	4.87	93.04	5.09	5.47
AUC0-[25 ng/mL]	(ng·h/mL)	3.81	1.79	47.06	3.67	2.25	61.25
Cmax	(ng/mL)	41.01	15.68	38.23	83.10	25.04	30.14
Tmax (Mean)	(h)	0.604	0.426	70.51	0.577	0.383	66.36
Tmax (Median)	(h)	0.417	0.446	-	0.459	0.334	-
T1/2max	(h)	0.202	0.062	30.88	0.252	0.100	39.79
T[25 ng/mL]	(h)	0.275	0.122	44.32	0.246	0.124	50.53
Kel	(h-1)	0.2792	0.0921	32.97	0.2818	0.0915	32.48
T½ el	(h)	2.75	0.91	32.87	2.73	0.93	34.14

The formulation was considered to have linear kinetics in healthy elderly subjects over the dose range studied if the 90% confidence intervals for the ratio (Treatment A (1.75 mg dose)/Treatment B (3.5 mg dose) were within the range of 80 to 125% for the AUC0-t, AUC0-inf, AUC0-4h, and Cmax.

The test 1.75 mg sublingual zolpidem tartrate tablet (Treatment A) is dose proportional to the reference 3.5 mg sublingual zolpidem tartrate tablet (Treatment B) in the dose range of 1.75 mg to 3.5 mg under fasting conditions in elderly subjects since all 90% geometric confidence intervals were within the acceptance range.

Following table provides primary pharmacokinetic parameter ratios and 90% confidence intervals.

Table 25: 1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A) vs 3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B) (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI	Intra-Subject CV
1.75 mg Sublingual Zolpidem Tartrate/ 3.5 mg Sublingual Zolpidem Tartrate	AUC_{0-t}	103.6	98.4	109.0	9.88%
	$AUC_{0-\infty}$	104.5	99.3	109.9	9.69%
	C_{max}	95.88	88.9	103.4	14.6%

Reviewer's re-analysis of the data showed similar 90% confidence interval (CI), as shown in the table below.

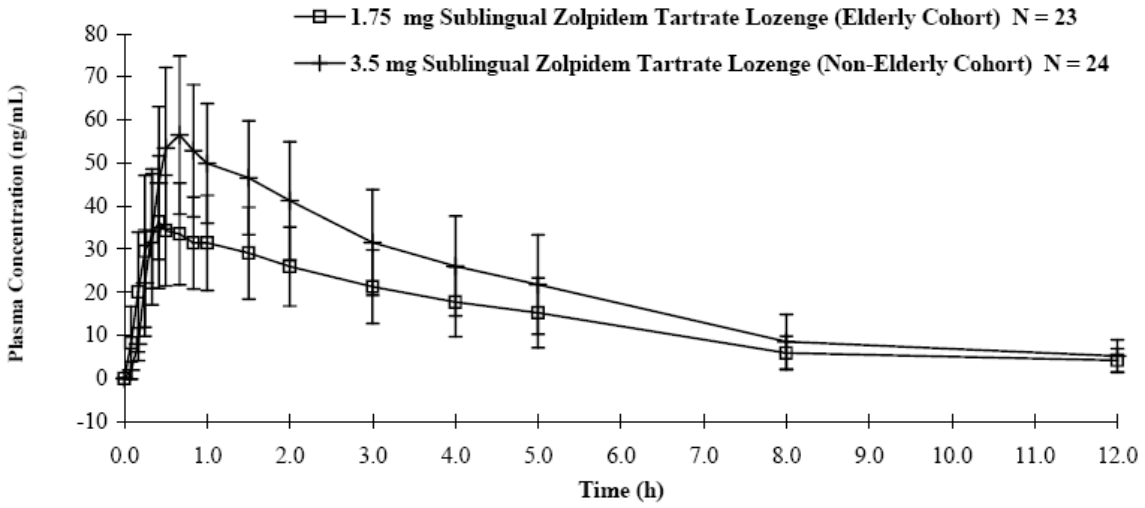
Table 26: 1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A) vs 3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B) (Reviewer's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI
1.75 mg Sublingual Zolpidem Tartrate/ 3.5 mg Sublingual Zolpidem Tartrate	$AUC_{0-\infty}$	104.5	99.4	109.9
	C_{max}	95.88	88.9	103.4

Parallel design — elderly cohort (1.75 mg dose) N = 23 and adult non-elderly cohort (3.5 mg dose) N= 24

The mean zolpidem plasma concentration (±SD) vs time profiles are in the figure below.

Figure 6: Mean zolpidem (± SD) plasma concentrations (ng/mL) vs time profiles



Following table represents PK parameters for different treatments.

Table 27: Summary of Pharmacokinetic Results - Zolpidem (N = 23 for Treatment A and N = 24 for Treatment B)

		1.75 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (A)			3.5 mg Sublingual Zolpidem Tartrate Tablet (Adult Non-Elderly Cohort) (B)		
Parameters		**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC0-t	(ng·h/mL)	164.90	73.33	44.47	242.37	101.13	41.72
AUC0-inf	(ng·h/mL)	181.31	87.76	48.41	262.99	121.04	46.02
AUC0-4h	(ng·h/mL)	100.50	36.06	35.89	149.67	44.36	29.64
AUCt/inf	(%)	92.30	4.41	4.78	93.59	4.09	4.37
AUC0-[25 ng/mL]	(ng·h/mL)	3.95	1.84	46.67	4.34	2.62	60.33
Cmax	(ng/mL)	40.66	15.41	37.90	61.87	15.77	25.50
Tmax (Mean)	(h)	0.621	0.424	68.29	0.760	0.388	51.09
Tmax (Median)	(h)	0.417	0.458	-	0.667	0.180	-
T1/2max	(h)	0.207	0.065	31.46	0.358	0.164	45.75
T[25 ng/mL]	(h)	0.287	0.129	45.09	0.369	0.149	40.52

Kel	(h-1)	0.2787	0.0900	32.28	0.2918	0.0935	32.05
T½ el	(h)	2.75	0.89	32.23	2.62	0.83	31.75

According to the protocol criteria, the bioavailability of the 1.75 mg sublingual zolpidem tartrate tablet in elderly subjects was considered similar to the bioavailability of the 3.5 mg sublingual zolpidem tartrate tablet in adult non-elderly subjects if the 90% confidence intervals for the AUC0-t ratio (elderly 1.75 mg versus adult non-elderly 3.5 mg) were within the range of 80 to 125%.

The bioavailability of the 1.75 mg sublingual zolpidem tartrate tablet in elderly subjects is less than the bioavailability of the 3.5 mg sublingual zolpidem tartrate tablet in non-elderly subjects under fasting conditions since the 90% confidence intervals for the AUC_{0-t} ratio (elderly 1.75 mg versus adult non-elderly 3.5 mg) were not within the 80 to 125% range.

The observed lower limit for of the 90% confidence interval for the AUC_{0-t} ratio was 53.62%, and the upper limit of the 90% confidence interval for the AUC_{0-t} ratio (elderly 1.75 mg versus adult non-elderly 3.5 mg) was 82.49%.

Following table provides primary pharmacokinetic parameter ratios and 90% confidence intervals.

Table 28: Bioequivalence anlaysis: Elderly Cohort 1.75 mg Sublingual Zolpidem Tartrate Tablet (A) vs Non-elderly Cohort 3.5 mg Sublingual Zolpidem Tartrate Tablet idem (B) (Sponsor's Analysis)

Treatment Comparisons	Parameter	Ratio	Lower 90% CI	Upper 90% CI	Intra-Subject CV
1.75 mg Sublingual Zolpidem Tartrate/ 3.5 mg Sublingual Zolpidem Tartrate	AUC_{0-t}	66.5	53.6	82.5	46.1%
	$AUC_{0-\infty}$	65.3	55.4	76.9	34.3%
	C_{max}	62.8	53.3	74.0	34.4%

Following table represents PK parameters and comparison between elderly and adult subjects receiving 3.5 mg sublingual zolpidem.

	3.5 mg Sublingual Zolpidem Tartrate Tablet (Elderly Cohort) (B)			**3.5 mg Sublingual Zolpidem Tartrate Tablet (Adult Non-Elderly Cohort) (B)**			
Parameters	**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**	**Means Ratio % (Elderly/**

								Adult)
AUC0-t	(ng·h/mL)	320.08	151.78	47.42	242.37	101.13	41.72	132.1
AUC0-inf	(ng·h/mL)	352.45	187.94	53.32	262.99	121.04	46.02	134.0
AUC0-4h	(ng·h/mL)	194.15	72.46	37.32	149.67	44.36	29.64	129.7
AUCt/inf	(%)	93.04	5.09	5.47	93.59	4.09	4.37	99.4
AUC0-[25 ng/mL]	(ng·h/mL)	3.67	2.25	61.25	4.34	2.62	60.33	84.6
Cmax	(ng/mL)	83.10	25.04	30.14	61.87	15.77	25.50	134.3
Tmax (Mean)	(h)	0.577	0.383	66.36	0.760	0.388	51.09	75.9
Tmax (Median)	(h)	0.459	0.334	-	0.667	0.180	-	68.8
T1/2max	(h)	0.252	0.100	39.79	0.358	0.164	45.75	70.4
T[25 ng/mL]	(h)	0.246	0.124	50.53	0.369	0.149	40.52	66.7
Kel	(h^{-1})	0.2818	0.0915	32.48	0.2918	0.0935	32.05	96.6
T½ el	(h)	2.73	0.93	34.14	2.62	0.83	31.75	104.2

The ratio of mean AUC and C_{max} of elderly subjects to adults indicate that the exposure is approximately 30% more in elderly subjects compared adults.

Conclusions

- The test 1.75 mg sublingual zolpidem tartrate tablet (Treatment A) is dose-proportional to the reference 3.5 mg sublingual zolpidem tartrate tablet (Treatment B) in the dose range of 1.75 mg to 3.5 mg under fasting conditions.

- The bioavailability of the 1.75 mg sublingual zolpidem tartrate tablet in elderly subjects in the elderly is less than that of the 3.5 mg dose in non-elderly subjects.

- Exposure (AUC and Cmax) to zolpidem was approximately 34% higher in elderly subjects compared to Adults given the same 3.5 mg dose.

Discussion and Labeling Recommendation

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative-hypnotic drugs and the difference (higher) in the exposure to zolpidem is a concern in the treatment of elderly. Therefore the recommended dose in elderly is half the adult dose (1.75 mg) similar to other zolpidem products including the reference Ambien®. C_{max} and $AUC_{0\text{-}inf}$ increased by 50% and 64% respectively in a

study (n=8) conducted in elderly subjects with the reference listed drug Ambien® (according to the approved label).

ZI-05-009: A Randomized, Double-Blind, Daytime, 4-Way Crossover Study to Evaluate the Pharmacokinetics, Dose Proportionality, Pharmacodynamics, and Safety and Tolerability of 3 Doses of Sublingual Zolpidem Tartrate Tablets Compared to Placebo in Normal Healthy Volunteers

Objectives:

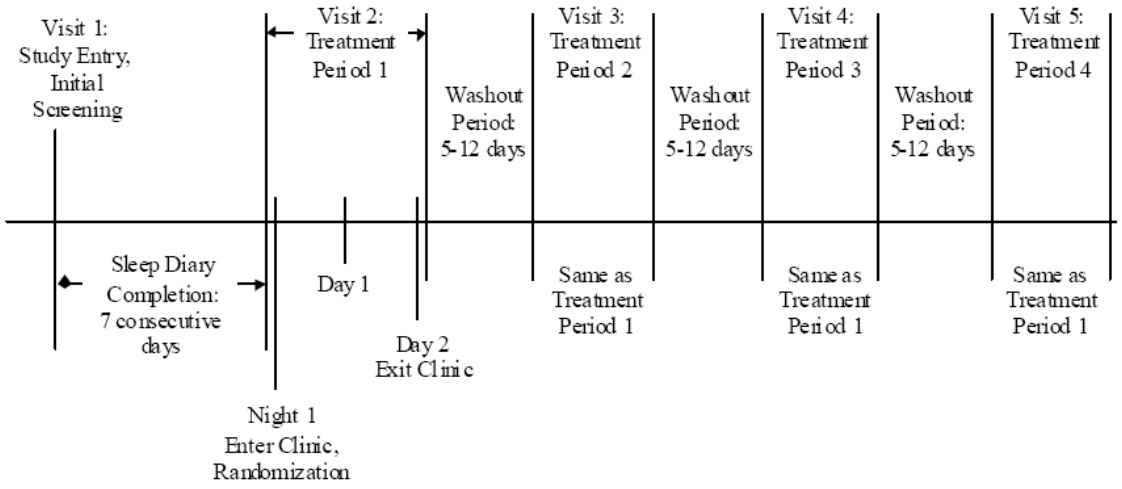
1. To evaluate the pharmacokinetics (PK) and dose-proportionality of zolpidem in healthy adults following sublingual administration of single doses of 1.0 mg, 1.75 mg, and 3.5 mg zolpidem tartrate tablets
2. To investigate the pharmacodynamics (PD) of zolpidem following sublingual administration of single doses of 1.0 mg, 1.75 mg, and 3.5 mg
3. To evaluate the safety and tolerability of zolpidem in healthy adults following sublingual administration of single doses of 1.0 mg, 1.75 mg, and 3.5 mg

Study Design	Single-centre, randomized, placebo-controlled, double-blind, daytime, 4-way crossover study
Study Population	Healthy male and female Age: 21- 45 years BMI: 18.0- 30.0 kg/m^2 24 subjects were randomized, and 24 completed the study
Treatment Groups	Treatment A = 1.0 mg sublingual zolpidem tartrate tablet Treatment B = 1.75 mg sublingual zolpidem tartrate tablet Treatment C = 3.5 mg oral zolpidem tartrate tablet Treatment D = Placebo oral zolpidem tartrate tablet
Methodology	Twenty-four (24) evaluable subjects were planned to each receive study drug on 2 successive days in each of 4 treatment periods. Subjects were randomly assigned to 1 of the 4 treatment sequences in accordance with a predetermined randomization schedule. In each treatment period, subjects were admitted at the clinic 1 day before the first dosing and practice-dosing with placebo (Treatment Period 1 only), baseline self-ratings, and psychomotor testing were performed. On the first treatment day of each period, subjects were awakened at 0700 and a Digit Symbol Substitution Test (DSST), a Choice Reaction Time (CRT), and a Symbol Copying Test (SCT) were performed, followed by a self-rating of sedation on a Visual Analog Scale (VAS), and a Buschke Memory Recall Test. Study drug was administered at 0800 after an overnight fast. The PD assessments were conducted over 5 hr. A standardized lunch was provided at

<table>
<tr><td></td><td colspan="2">1300, after the hr 5 PD performance tests. A standardized dinner was provided at 1800 and lights out was at 2200. On the second treatment day of each period, subjects were awakened at 0700 and study drug was administered at 0800 after an overnight fast. Blood samples were drawn for PK analyses over 12 hr. A standardized lunch was provided at 1300, after the hr 5 PK sample had been collected. A standardized dinner was provided at 1800 and subjects were released from the unit at 2000. There was a washout of at least 5 days, but no longer than 12 days, between treatment periods. The duration of the washout period was measured from the last day of the preceding period to the first day of the subsequent period.</td></tr>
<tr><td>Dosage and Administration</td><td>Reference Product
TransOral placebo sublingual tablet</td><td>TestProduct
TransOral zolpidem tartrate sublingual tablet 1.0 mg
TransOral zolpidem tartrate sublingual tablet 1.75 mg
TransOral zolpidem tartrate sublingual tablet 3.5 mg</td></tr>
<tr><td>Sampling: Blood</td><td colspan="2">Blood samples were collected prior to study drug administration (pre-dose) and at 5, 10, 20, 30, 45, and 60 minutes, and 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 h post-dose in each period.</td></tr>
<tr><td>Analysis</td><td colspan="2">Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 0.25 ng/mL.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>0.75, 9.38, 18.75, and 43.75 ng/mL</td><td>0.25, 0.5, 2.5, 12.5, 25, 37.5, 50, and 62.5 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.04 to 6.67</td><td>3.08 to 4.0</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.9958</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">0.25 to 62.5 ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">0.25 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td colspan="2">None</td></tr>
<tr><td>Feces</td><td colspan="2">None</td></tr>
<tr><td>PK Assessments</td><td colspan="2">The following PK parameters were calculated: Cmax, tmax, AUC0-t, AUC0-inf, Kel, t½, and partial AUCs (partial AUCs calculated at 0 to 5 min, 0 to 10 min, 0 to 20 min, 0 to 30 min, 0 to 45 min, 0 to 1.0 hr, 0 to 1.5 hr, 0 to 2.0 hr, 0 to 2.5 hr, 0 to 3.0 hr, 0 to 4.0 hr, 0 to 5.0 hr, 4.0 to 5.0 hr). Descriptive statistics (N, mean, standard deviation,</td></tr>
</table>

	minimum, median, maximum, geometric mean, and coefficient of variation) were used to summarize the PK parameters for each treatment.
PD Assessments	For all PD variables, all postdose scores were assessed as an increment or decrement relative to the predose values. Each time point was evaluated separately relative to the baseline value. Area under the time-effect curve for the effect change score versus time was calculated for each of the following time intervals: 0 to 2 hr, 0 to 4 hr, 2 to 4 hr, and 4 to 5 hr.
Statistical Methods	One analysis population was analyzed for this study, the intent-to-treat population. The intent-to-treat population is defined as all randomized subjects who received at least 1 dose of study drug. All safety, PK, and PD analyses were based upon the intent-to-treat population.

Following figure represents the study design schematic for this study



RESULTS:

A summary of mean (SD) zolpidem PK parameters of the sublingual zolpidem 3.5, 1.75 and 1.0 mg treatment groups is presented in the table below.

Mean (SD) Zolpidem Plasma Pharmacokinetic Parameters After Single Dose Administration of Zolpidem 3.5, 1.75 and 1.0 mg

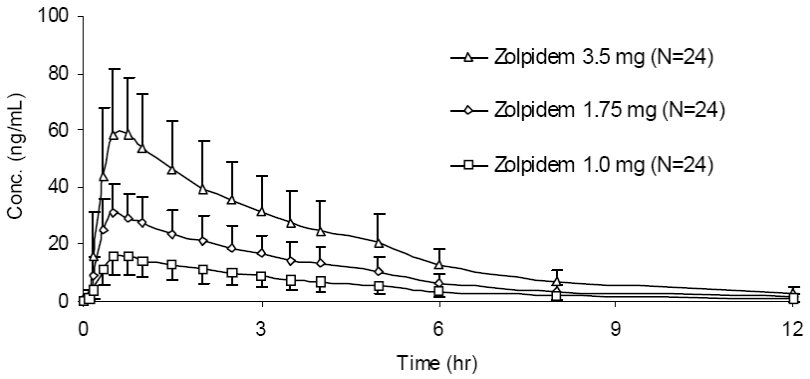
	Treatment		
Parameter	**Zolpidem 3.5 mg (N=24)**	**Zolpidem 1.75 mg (N=24)**	**Zolpidem 1.0 mg (N=24) a**
Cmax (ng/mL)	64.14 (22.35)	32.17 (10.38)	17.03 (6.84)
tmax (h)	0.631 (0.205)	0.632 (0.268)	0.575 (0.211)

AUC0-t (ng.h/mL)	229.48 (91.89)	119.55 (48.96)	62.59 (29.08)
AUC0-inf (ng h/mL)	242.57 (100.37)	126.10 (53.39)	66.16 (31.49)
t½ (h)	2.45 (0.580)	2.43 (0.597)	2.33 (0.790)

Mean C_{max} PK parameters after sublingual zolpidem 3.5 mg, 1.75 and 1.0 mg treatment were 64.14, 32.17 and 17.03 ng/mL, respectively; the mean AUC_{0-t} and AUC_{0-inf} were 229.48 ng.h/mL and 242.57 ng.h/mL, 119.55 and 126.10 ng.h/mL and 62.59 and 66.16 ng.h/mL, respectively. After zolpidem 3.5 mg, 1.75 and 1.0 mg treatment, the mean t_{max} (0.631, 0.632 and 0.575 hr, respectively) and terminal half-life (2.45, 2.43 and 2.33 hr, respectively) were comparable.

Following figure represents the mean (SD) plasma concentration-time profiles of sublingual zolpidem in the 1.0, 1.75, and 3.5 mg treatment groups.

Mean (SD) Zolpidem plasma concentration-time profiles after administration of zolpidem 3.5, 1.75 and 1.0 mg.



An analysis of variance (ANOVA) was performed on ln-transformed dose-normalized (dose normalized to 1.0 mg) values of C_{max}, AUC_{0-t}, and AUC_{0-inf}. The 2 one-sided hypotheses were tested at the 5% level for ratio of means (1.0 mg/1.75 mg, 1.0 mg/3.5 mg and 1.75 mg/3.5 mg) and 90% geometric confidence interval for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data, for C_{max}, AUC_{0-t}, and AUC_{0-inf}.

A summary of the statistical analyses of zolpidem PK parameters after administration of sublingual zolpidem 3.5, 1.75 and 1.0 mg are presented in the following table:

ANOVA Analysis of Zolpidem Plasma Pharmacokinetic Parameters After Administration of Zolpidem 1.0, 1.75 and 3.5 mg

	Test/Reference Geometric Mean Ratio (%) (90% confidence interval) (N=24)

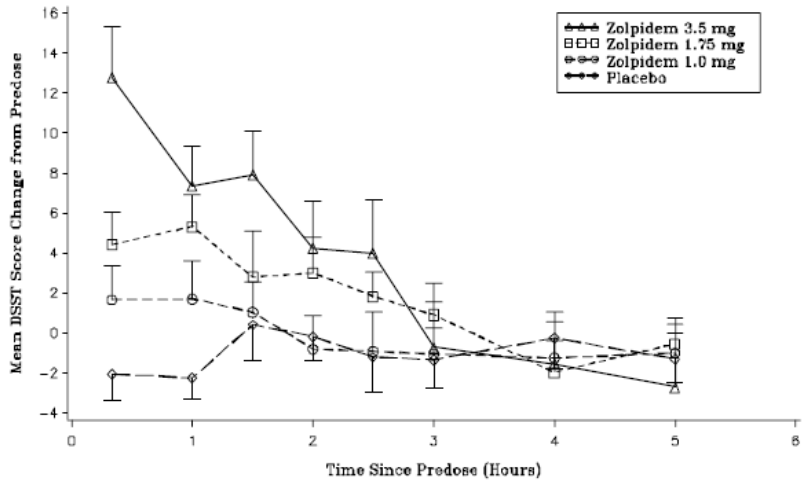
Test	Reference	Cmax	AUC0-t	AUC0- inf
Zolpidem 1.0 mg	Zolpidem 1.75 mg	90.22 (79.69-102.14%)	88.23 (74.92-103.89%)	88.51 (75.15-104.25%)
Zolpidem 1.0 mg	Zolpidem 3.5 mg	90.90 (80.29-102.91%)	90.79 (77.10-106.91%)	90.98 (77.24-107.16%)
Zolpidem 1.75 mg	Zolpidem 3.5 mg	100.75 (88.99-114.06%)	102.91 (87.39-121.18%)	102.79 (87.27-121.07%)

Pharmacodynamic Results

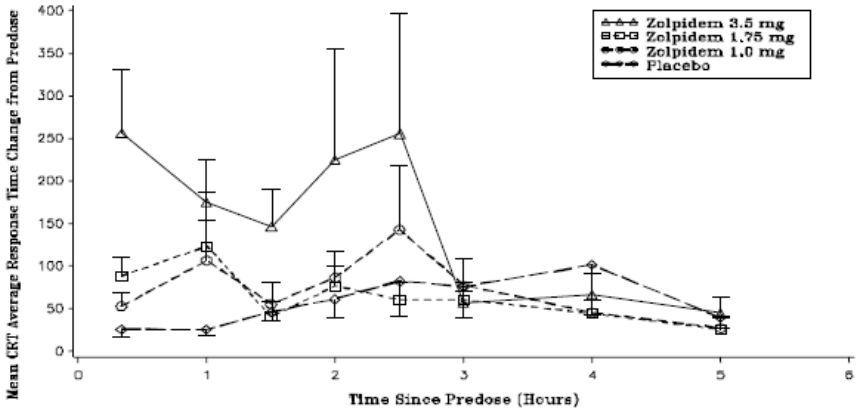
Pharmacodynamic aspects of this study will be reviewed in detail by medical officer.

Following figures represent pharmacodynamic endpoints measured at different times after zolpidem and placebo treatment.

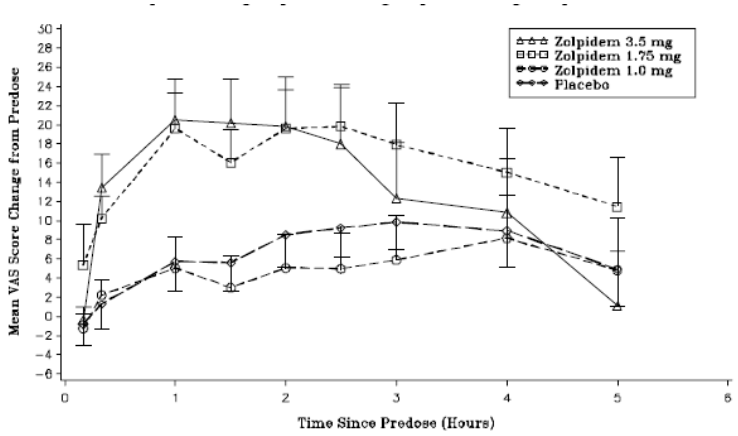
Mean DSST score change from predose by timepoint following administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo.



Mean Choice Reaction Time (CRT) average response time change from predose by timepoint following administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo



Mean VAS score change from predose by timepoint after administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo.



Relationship between PK and PD results

PK and PD data showed dose-response relationship in that the degree and duration of PD effects on the performance tests and sedation measures (Visual Analog Scale (VAS), Digit Symbol Substitution Test (DSST), Symbol Copying Test (SCT), Choice Reaction Time (CRT)) were highest in the 3.5 mg group and lowest in the 1.0 mg group, and were associated dose dependently with zolpidem plasma concentration levels and AUCs. Pharmacodynamic effects were highest for 3.5 mg zolpidem dose group. In this group, the tmax for pharmacodynamic endpoint was 0.0631 hr, and the largest differences in mean change from predose for the DSST, CRT average response time, and CRT number of errors occurred at the evaluation timepoints closest to the tmax.

Conclusions

- PK parameters (Cmax, AUC0-t, and AUC0-inf) were dose proportional for zolpidem 1.75 and zolpidem 3.5 mg treatments; the least-squares geometric mean ratio and 90% CIs for the least-squares geometric mean ratio for Cmax and AUC0-t and AUC0-inf were within 80% to 125%

- The PK parameters after the 1.0 mg zolpidem treatment were approximately dose proportional for C_{max} and $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$. However, lower limits of 90% CIs were below 80%.

ZI-16: A study to evaluate the pharmacodynamic (PD) effects of orally administered zolpidem tartrate tablets (Intermezzo® 3.5 mg) as assessed by the Digit Symbol Substitution Test (DSST)

Objectives:

Primary objectives

To evaluate the PD effects by DSST of a single oral dose of 3.5 mg zolpidem tartrate vs. placebo.

Secondary Objectives

1. To evaluate the PD effects as assessed by DSST of a single dose 3.5 mg zolpidem tartrate lozenge following sublingual administration.
2. To compare the PD effects as assessed by DSST of oral administration (p.o.) vs. sublingual route of administration of the 3.5 mg zolpidem tartrate lozenge.
3. To evaluate the safety and tolerability of zolpidem in healthy adults following p.o. and sublingual administration of the 3.5 mg of zolpidem tartrate lozenge.

In addition, the plasma concentration of zolpidem was assessed pre-dose and at 1, 3, 4, and 5 hours post-dose for safety purposes and to provide an evaluation of the pharmacokinetic-pharmacodynamic (PK-PD) relationship during the time period of interest for the DSST outcomes.

Study Design	This was a single center, double-blind, double-dummy, single-dose, randomized, three-period, six-sequence, crossover PD study.	
Study Population	Healthy male and female Age: 18-64 years BMI: 18.0- 32.0 kg/m^2 30 subjects (20 females and 10 males)	
Treatment Groups	Treatment A = 3.5 mg zolpidem tartrate lozenge p.o. followed by sublingual administration of placebo Treatment B = placebo p.o. followed by sublingual administration of 3.5 mg zolpidem tartrate lozenge Treatment C = placebo p.o. followed by sublingual administration of placebo The treatment phases were separated by washout periods of 5-7 days.	
Dosage and Administration	**Placebo** **-**Placebo lozenge - single dose, oral or sublingual administration	**Test: zolpidem tartrate lozenge (Intermezzo®)** - 3.5 mg, lozenge - single dose, oral or sublingual administration
Sampling: Blood	Blood samples for plasma zolpidem analysis were obtained immediately after performing DSST at baseline (pre-dose) and 1, 3, 4, and 5 hours post-dose in each period.	

<table>
<tr><td>Analysis</td><td>Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 1 ng/mL.

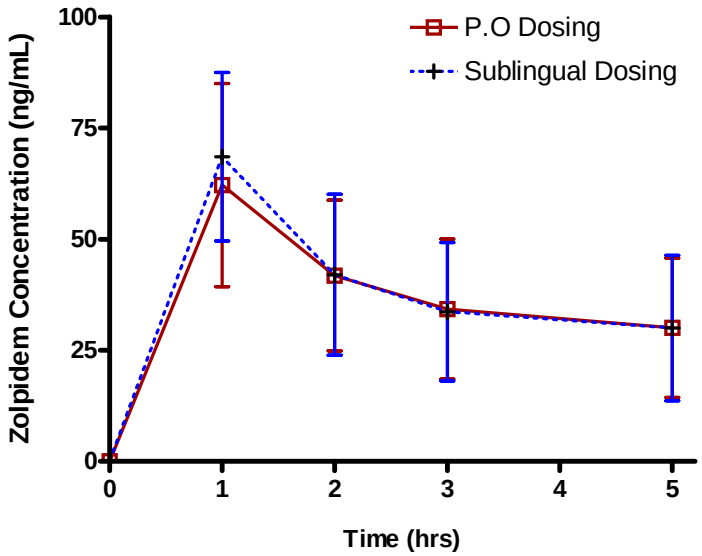
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>3.0, 25, 75, and 175 ng/mL</td><td>1, 2, 5, 50, 100, 200, and 250 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.59 to 4.27</td><td>2.68 to 4.41</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.996</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">1 to 250ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td>None</td></tr>
<tr><td>Feces</td><td>None</td></tr>
<tr><td>PK Assessments</td><td>No pharmacokinetic parameter was estimated during the study</td></tr>
<tr><td>PD Assessments</td><td>Primary (DSST change from baseline scores at each time point); Secondary (AUC_{0-5h}, AUC_{1-5h}, AUC_{3-5h}, AUC_{4-5h}, AUC_{3-4h}, $AUC_{0-10min}$, $AUC_{0-20min}$, and $AUC_{0-40min}$)</td></tr>
<tr><td>Statistical Methods</td><td>Pharmacodynamics:
• Parametric ANOVA on DSST change from baseline scores at each time point and on AUC_{0-5h}, AUC_{1-5h}, AUC_{3-5h}, AUC_{4-5h}, AUC_{3-4h}, $AUC_{0-10min}$, $AUC_{0-20min}$, and $AUC_{0-40min}$;
• Factors incorporated in the model included sequence, period, and treatment as fixed effects and subject(sequence) as a random effect;
• Pairwise comparisons (3.5 mg zolpidem tartrate lozenge p.o. vs. placebo, 3.5 mg sublingual zolpidem tartrate lozenge vs. placebo, and 3.5 mg zolpidem tartrate lozenge p.o. vs. 3.5 mg sublingual zolpidem tartrate lozenge) at the 5% level of significance.

Pharmacokinetics:
Zolpidem plasma concentrations at each time point were summarized for the two zolpidem tartrate administration modes (p.o. or sublingual) using descriptive statistics. No PK parameter was estimated during the study. No statistical test comparing concentration or PK parameters for the two zolpidem tartrate administration modes was conducted during the study.</td></tr>
</table>

RESULTS:

Following figure represents PK profiles for both treatments of zolpidem formulations (sublingual and p.o dosing).

Mean (SD) plasma zolpidem concentrations time profile obtained after sublingual and p.o dosing.



Reviewer's comment: PK sampling time points were inadequate to quantitate the absorption differences between sublingual and oral administration.

Detailed review of pharmacodynamics section will be provided by medical officer assigned to this NDA submission.

When compared to placebo group at 0, 20, and 40 minutes and at 1 hour post-dose DSST scores were significantly decreased in both the sublingual and p.o. dosage groups. At 3 hrs and 5 hrs DSST scores for treatment groups did not differ significantly from placebo group. There were no statistically significant differences between 3.5 mg zolpidem tartrate lozenge p.o. and 3.5 mg sublingual zolpidem tartrate lozenge in any of the PD parameters.

Following figure represents mean DSST change from baseline score in different treatment groups.

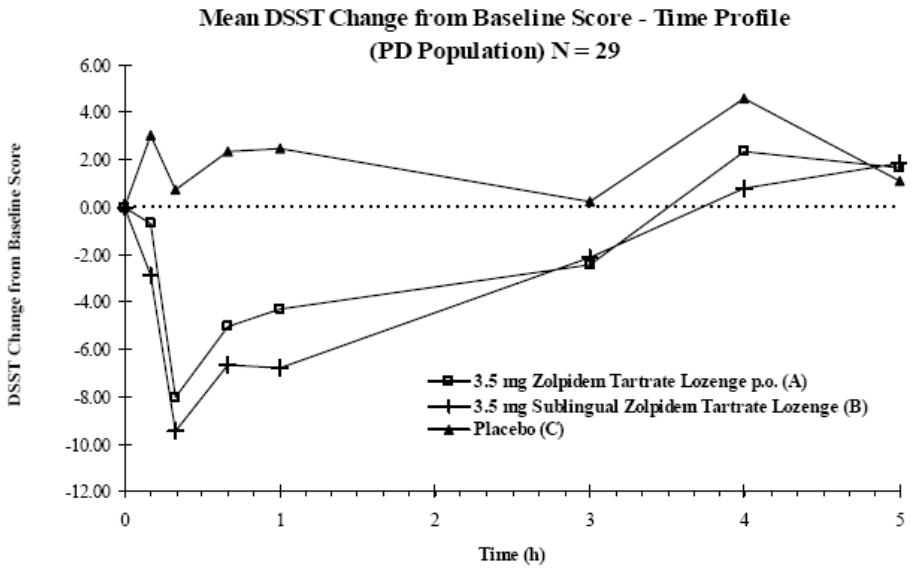
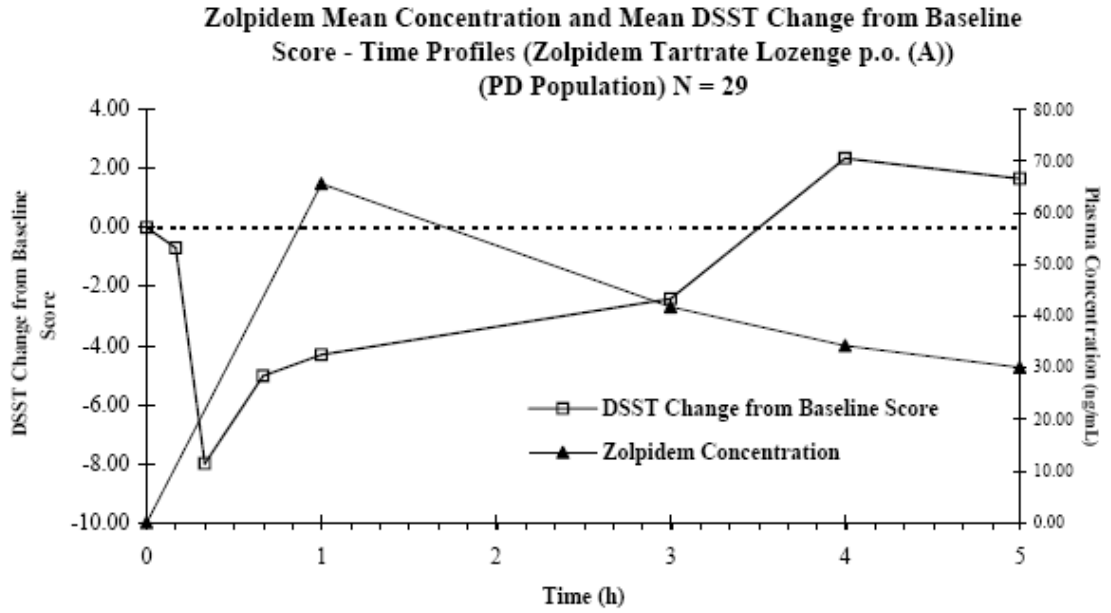


Table below represents area under the DSST score vs time curve calculated at different time points for the treatments.

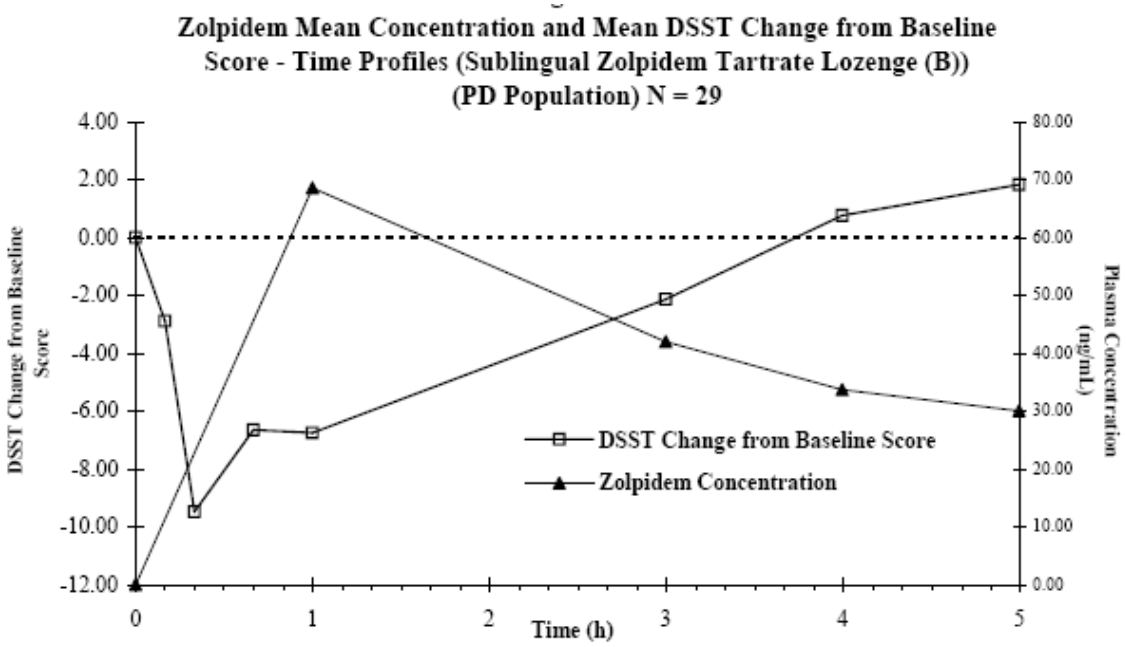
Table 29: Area Under the DSST Change from Baseline Score - Time Curve Analysis N = 29 (PD Population)

Parameter	Means (Score·h)			Comparisons P-values		
	3.5 mg Zolpidem Tartrate Lozenge p.o. (A)	3.5 mg Sublingual Zolpidem Tartrate Lozenge (B)	Placebo (C)	Primary	Secondary	
				A vs C	B vs C	A vs B
$AUC_{0\text{-}10min}$	-0.05	-0.23	0.26	0.0131	0.0002	0.1690
$AUC_{0\text{-}20min}$	-0.88	-1.29	0.62	<0.0001	<0.0001	0.2579
$AUC_{0\text{-}40min}$	-2.73	-3.95	1.07	<0.0001	<0.0001	0.1494
$AUC_{0\text{-}5h}$	-9.05	-14.48	9.75	0.0045	0.0005	0.4532
$AUC_{1\text{-}5h}$	-4.76	-8.29	7.88	0.0246	0.0058	0.5790
$AUC_{3\text{-}5h}$	1.97	0.60	5.22	0.2335	0.1119	0.6825
$AUC_{4\text{-}5h}$	2.00	1.29	2.83	0.5380	0.3186	0.7004
$AUC_{3\text{-}4h}$	-0.03	-0.69	2.40	0.0933	0.0399	0.6930

Following figure represents mean DSST change from baseline for sublingual zolpidem tartrate tablet given p.o in relation to the plasma zolpidem concentration



Following figure represents mean DSST change from baseline for zolpidem tartrate lozenge in relation to the plasma zolpidem concentration



The lowest DSST scores were recorded at 20, 40 and 60 minutes which correspond to the increasing plasma zolpidem concentrations upto 60 min for both the active treatments.

Conclusions

- Pharmacokinetic profile appears to be similar for both sublingual and p.o dosing

- The DSST scores were lowest at the peak zolpidem concentration.

ZI-17: A two part study in healthy adult volunteers to assess the comparative early pharmacokinetic (PK) parameters and pharmacodynamic (PD) effects of the zolpidem tartrate 3.5 mg sublingual tablet and the oral zolpidem tartrate 3.5 mg tablet; and to describe the PK dose proportionality between the oral zolpidem tartrate 10mg (Ambien®) and 3.5mg tablets

Objectives:

The objectives for Part I of the study were:

- To compare the PK profile of the zolpidem tartrate 3.5 mg sublingual tablet with the oral zolpidem tartrate 3.5 mg tablet; including evaluating the early differences in the PK profile between the two formulations.
- To evaluate the early (20 minutes) sedative PD effects of the zolpidem tartrate 3.5 mg sublingual tablet compared to the oral zolpidem tartrate 3.5 mg tablet as assessed by relative electroencephalographic amplitude in the beta frequency range (EEG) and Digit Symbol Substitution Test (DSST).
- To compare the sedative PD effects as assessed by ß EEG and DSST of the zolpidem tartrate 3.5 mg sublingual tablet to the oral zolpidem tartrate 3.5 mg tablet.

The objective for Part II of the study was to describe the single-dose PK dose proportionality of 10 mg oral zolpidem tartrate tablets (Ambien®) to oral zolpidem tartrate 3.5 mg tablets in healthy, adult subjects.

The safety objective was to assess the safety and tolerability of the zolpidem tartrate 3.5 mg sublingual tablet against that of the oral zolpidem tartrate 3.5 mg tablet.

Study Design	Part I was a single center, double-blind, double-dummy, randomized, placebo-controlled, three-period, six-sequence, crossover PK/PD study. Part II was a single center, open-label, single-dose PK study. Following a washout period of 2 to 5 days after the third period of Part I of the study
Study Population	Healthy male and female Age: 18-45 years BMI: 18.0- 32.0 kg/m^2 36 subjects (10 females and 26 males) 34 subjects completed the study
Treatment Groups	Treatment A = oral zolpidem tartrate 3.5 mg tablet followed by sublingual placebo tablet Treatment B = oral placebo tablet followed by zolpidem tartrate 3.5 mg sublingual tablet

<table>
<tr><td></td><td colspan="2">Treatment C = oral placebo tablet followed by sublingual placebo tablet
The treatment phases were separated by washout periods of 5±2 days.</td></tr>
<tr><td>Dosage and Administration</td><td>Placebo
-Placebo tablet
- single dose, oral or sublingual administration

Reference
- Oral zolpidem tartrate tablet (Ambien®)
- 10 mg single dose, fasted conditions</td><td>Test: zolpidem tartrate tablet (Intermezzo®)
- 3.5 mg, zolpidem tablet
- 3.5 mg zolpidem tablet
- single dose, oral or sublingual administration
- Fasted conditions</td></tr>
<tr><td>Treatment Instructions</td><td colspan="2">For the sublingual administration, the subjects were instructed to place the drug tablet under the tongue, where it dissolved in one or two minutes; to move the tablet around with their tongue to help the tablet dissolve more quickly, and to avoid any swallowing for the first two minutes. Subjects signaled to the clinical staff when the tablet had dissolved. An oral cavity examination was performed no later than 10 minutes after the subject signaled dissolution was completed.</td></tr>
<tr><td>Sampling: Blood</td><td colspan="2">Blood samples for plasma zolpidem analysis were obtained at baseline (pre-dose) and 5, 10, 15, 20, 25, 30, 35, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours post-dose.</td></tr>
<tr><td>Analysis</td><td colspan="2">Zolpidem concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 1 ng/mL.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (µg/mL)</td><td>3.0, 6, 75, and 175 ng/mL</td><td>1, 2, 1.2, 25, 50, 100, 200, and 250 ng/mL</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.35 to 4.51</td><td>2.83 to 3.86</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.995</td></tr>
<tr><td>Linear Range (µg/mL)</td><td colspan="2">1 to 250ng/mL</td></tr>
<tr><td>Sensitivity (LLOQ, µg/mL)</td><td colspan="2">1 ng/mL</td></tr>
</table></td></tr>
<tr><td>Urine</td><td colspan="2">None</td></tr>
<tr><td>Feces</td><td colspan="2">None</td></tr>
<tr><td>PK Assessments</td><td colspan="2">Part I (Comparison 3.5 mg zolpidem tartrate formulations [tablet and sublingual tablet]):

Primary (AUC0-inf and Cmax);
Secondary (AUC0-20 min, AUC0-4h, T1/2 el, and Tmax).</td></tr>
</table>

	Part II (Comparison 3.5 mg and 10 mg oral zolpidem tartrate tablets): AUC0-t, AUC0-inf, and Cmax.
PD Assessments	Primary: Area under the EEG change from baseline scores from 0 to 21 minutes (AUCE0-21min); Secondary: The EEG and DSST scores at each time point, the EEG and DSST change from baseline scores at critical time points, and the areas under the EEG and DSST change from baseline score - time curve from time 0 to 21 minutes (AUCE0-21min) for EEG and 0 to 20 minutes (AUCE0-20min) for DSST, and partial AUCE up to 8 hours (~481 minutes) were the PD parameters calculated in this study.

Note: This study utilized 3.5 mg zolpidem tartrate sublingual tablet and a 3.5 mg oral zolpidem tartrate tablet as a comparator formulated specifically for this study. (b) (4)

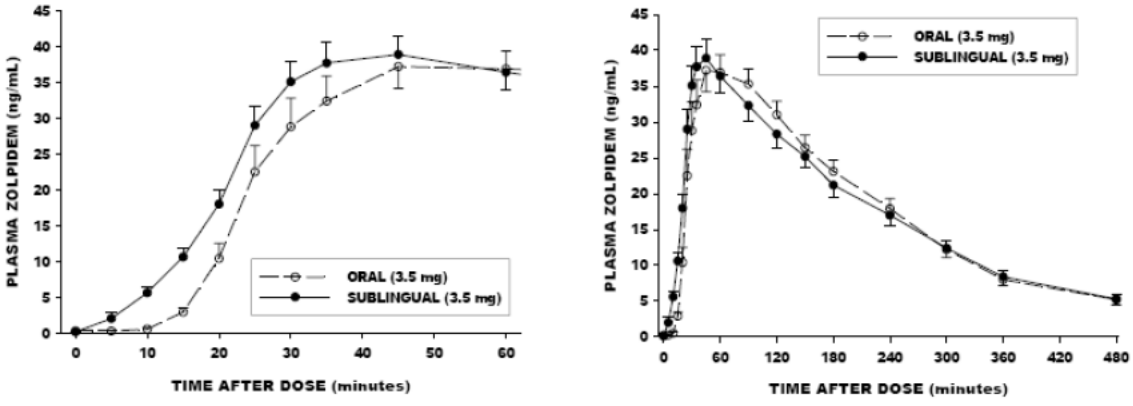
he analytical procedures used to test for the release of 3.5 mg oral zolpidem tartrate tablet, were from the compendial methods as described in USP and EP (impurity test).

RESULTS:

Detailed review of pharmacodynamics section will be provided by medical officer assigned to this NDA submission. PD evaluation was done through EEG and DSST.

Part I: 3.5 mg oral zolpidem tartrate tablet and 3.5 mg sublingual zolpidem tartrate tablet

Mean (±SE, n=35) plasma zolpidem concentrations for Study Part I. left: 0-60 minutes; right: 0-480 minutes.



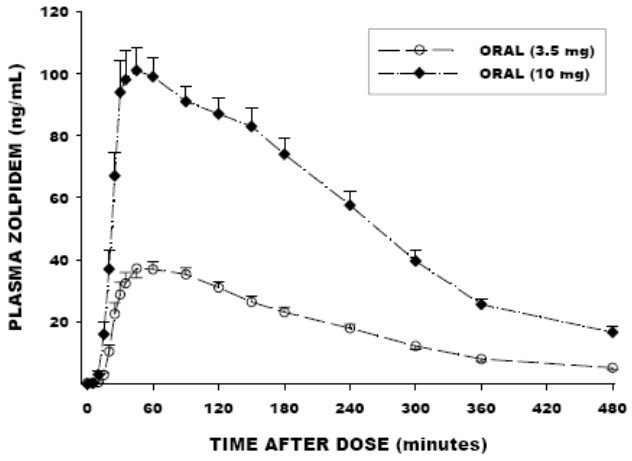
Absorption of zolpidem was faster from 3.5 mg sublingual tablet when compared to 3.5 mg oral zolpidem. However, systemic exposure, in terms of Cmax and AUC, was similar for the two formulations in this study.

Summary of Zolpidem Kinetic Variables for Comparison of Oral and Sublingual 3.5 mg Doses (Study Part I).

	Mean (±SE) value		Sublingual/oral ratio	
	3.5 mg oral	3.5 mg sublingual	Arithmetic mean (±SE)	Geometric mean (90% CI)
C_{max} (ng/mL)	46.0 (±2.9)	43.8 (±2.7)	1.03 (±0.06)	0.95 (0.84-1.08)
AUC (ng/mL x hr)				
0-20 min	0.74 (±0.16)*	2.27 (±0.26)*	–	–
0-infinity	161.5 (±12.0)	170.0 (±16.6)	1.06 (±0.05)	1.02 (0.94-1.11)
$t_{½}$ (hr)	2.1 (±0.11)	2.5 (±0.40)	–	–

Part II: 3.5 mg oral zolpidem tartrate tablet and 10 mg oral zolpidem tartrate tablet

Bioequivalence was evaluated between a 3.5 mg oral zolpidem tartrate tablet and a 10 mg oral zolpidem tartrate tablet (Ambien) using dose-normalized data to the 3.5 mg dose. Both formulations are bioequivalent in terms of rate and extent of absorption as shown in the figure below.



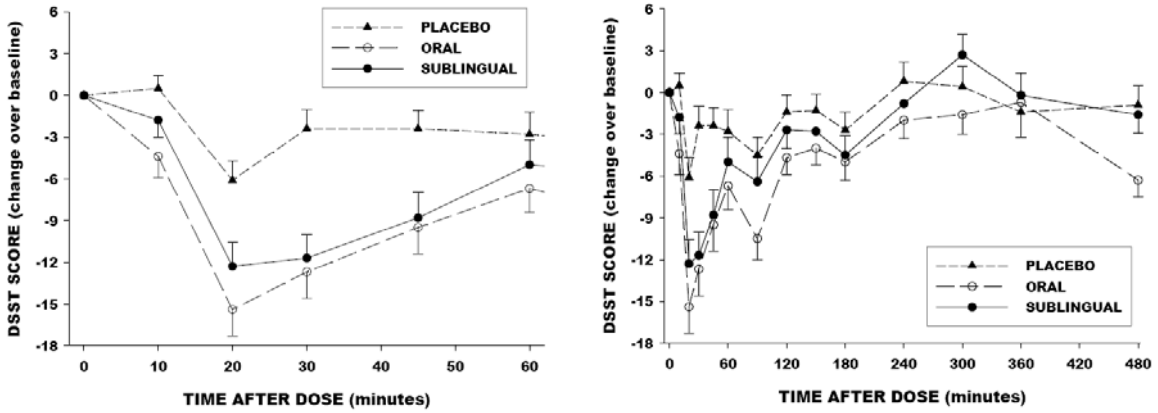
Summary of Zolpidem Kinetic Variables for Comparison of 3.5 mg and 10 mg Oral Doses (Study Part II).

	Mean (±SE)		3.5 mg/10 mg ratio	
	3.5 mg oral	10 mg oral	Arithmetic mean (±SE)	Geometric mean (90% CI)
C_{max} (ng/mL)	45.5 (±2.9)	129.6 (±6.9)	–	–
C_{max} (ng/mL per mg)	13.0 (±0.8)	13.0 (±0.7)	1.03 (±0.46)	0.98 (0.90-1.07)
AUC (ng/mL x hr)	162.2 (±12.0)	486.0 (±35.8)	–	–
AUC (ng/mL x hr per mg)	46.3 (±3.4)	48.6 (±3.6)	0.99 (±0.34)	0.95 (0.88-1.03)
$t_{½}$ (hr)	2.1 (±0.1)	2.1 (±0.1)	–	–

Digit-Symbol Substitution Test (DSST)

A DSST test was used to measure complex psychomotor activity, short-term memory, and fine motor control. The DSST was practiced three times prior to each study trial day. The test was done twice prior to test drug administration, and at multiple post-dosage times. The two pre-dose scores (number correct in 1.5 minutes) were averaged and used as the baseline value. All postdosage scores were expressed as the increment or decrement over the pre-dose baseline.

Mean (±SE, n=35) change over baseline in percent beta EEG amplitude. left: 0-61 minutes; right: 0-481 minutes.



Conclusions

- Absorption was faster from sublingual zolpidem and earlier exposure 0-20 minutes was higher when compared to oral zolpidem tablet. DSST change however was similar or greater for oral zolpidem tablet.
- The overall exposure (Cmax and AUC) was similar for (sublingual zolpidem tablet and oral zolpidem tablet) two formulations.
- Both formulations (3.5 mg oral zolpidem tablet and 10 mg Ambien®) were bioequivalent.

- There was a significant difference between active treatments and placebo, but no significant difference between active treatments for various intervals after dosage. However, change in DSST score from baseline appears to be higher for oral administration compared to sublingual administration at several time points.

ZI-04-001-001: Single Dose Three-Way Fixed Sequence Pilot Fasted Bioavailability Study of Zolpidem 10 mg Tablets and Powder in Healthy Volunteers

Objectives:

The purpose of this study was to determine the pharmacokinetic profiles of sponsor's Zolpidem 10 mg tablet after administration of single doses, using different swallowing times, to normal healthy subjects under fasted conditions and to use the data to design a pivotal study.

Study Design	Single-centre, single-dose, three-way, fixed sequence study
Study Population	Healthy male and female Mean Age: 29 (20 to 37) years 8 subjects (5 men and 3 women)
Treatment Groups	Treatment 1 = Zolpidem tartrate transmucosal tablet, 10 mg Treatment 2 = Zolpidem tartrate transmucosal tablet, 10 mg Treatment 3 = Zolpidem tartrate transmucosal tablet, 10 mg
Treatment Instructions	Subjects were required to rinse their mouth with about 240 ml of drinking water prior to dosing. The powdered transmucosal tablet was placed under the tongue until it dissolved. For treatment 1, subjects swallowed saliva every two (2) minutes over 10 minutes (5 blocks of 2 minutes). For treatment 2, subjects swallowed saliva every five (5) minutes over 10 minutes (2 blocks of 5 minutes). For treatment 1, subjects swallowed saliva only 10 minutes after drug administration
Dosage and Administration	- 10 mg, powdered transmucosal tablet - single dose, under fasting condition
Sampling: Blood	Blood samples were collected prior to study drug administration (pre-dose) and at 5, 8, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 180, 240, and 480 minutes (min) post-dose in each period.
Urine	None
Feces	None
PK Assessments	AUC_{0-t}, AUC_{0-inf}, C_{max} and Tmax
PD Assessments	None
Statistical Methods	The pharmacokinetic parameter estimates, as well as the concentrations at each scheduled sample time were evaluated by

	analysis of variance. Hypothesis testing in the analysis was conducted at $\alpha = 0.05$. Confidence Intervals (90%) for the area and peak concentration comparisons were calculated by the t-test approach (2,1-sided) at $\alpha = 0.10$ overall, $\alpha = 0.05$ each side:

RESULTS:

Summary of statistical comparisons of zolpidem results for 10 mg zolpidem powdered transmucosal tablets dosed by swallowing every 2 minutes (2-Min) and dosed by swallowing every 5 minutes (5-Min) when administered as a single 10 mg dose after an overnight fast to 8 subjects.

Parameter	Least-Squares Means [1] 2-Min	5-Min	Ratio [2]	Power [3]	90% Confidence Interval [4] Lower	Upper
AUC 0-t (ng-min/ml)	35489	39591	0.896	0.59	0.746	1.047
Cmax (ng/ml)	160	168	0.954	0.66	0.817	1.092
Tmax (minutes)	72.5	76.6	0.946	0.10	-	-
Ln-Transformed:						
AUC 0-t (ng-min/ml)	32781	36737	0.892	0.68	0.768	1.037
Cmax (ng/ml)	154	162	0.952	0.67	0.817	1.109

1. Least-squares geometric means for ln-transformed data.
2. Ratio calculated as 2-Min least-squares mean divided by the 5-Min least-squares mean. None of the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the 5-Min mean or a ratio of 1.25 (ln-transformed results).
4. Confidence interval on the ratio.

Summary of statistical comparisons of zolpidem results for (b) (4) 10 mg zolpidem powdered transmucosal tablets dosed by swallowing every 2 minutes (2-Min) and dosed by swallowing once at 10 minutes (10-Min) when administered as a single 10 mg dose after an overnight fast to 8 subjects.

Parameter	Least-Squares Means [1] 2-Min	10-Min	Ratio [2]	Power [3]	90% Confidence Interval [4] Lower	Upper
AUC 0-t (ng-min/ml)	35489	40921	0.867	0.61	0.722	1.013
Cmax (ng/ml)	160	172	0.933	0.68	0.798	1.067
Tmax (minutes)	72.5	66.9	1.084	0.09	-	-
Ln-Transformed:						
AUC 0-t (ng-min/ml)	32781	39408	0.832*	0.68	0.716	0.966
Cmax (ng/ml)	154	167	0.923	0.67	0.792	1.076

1. Least-squares geometric means for ln-transformed data.
2. Ratio calculated as 2-Min least-squares mean divided by the 10-Min least-squares mean.
3. Power to detect a difference of 20% of the 10-Min mean or a ratio of 1.25 (ln-transformed results).
4. Confidence interval on the ratio.

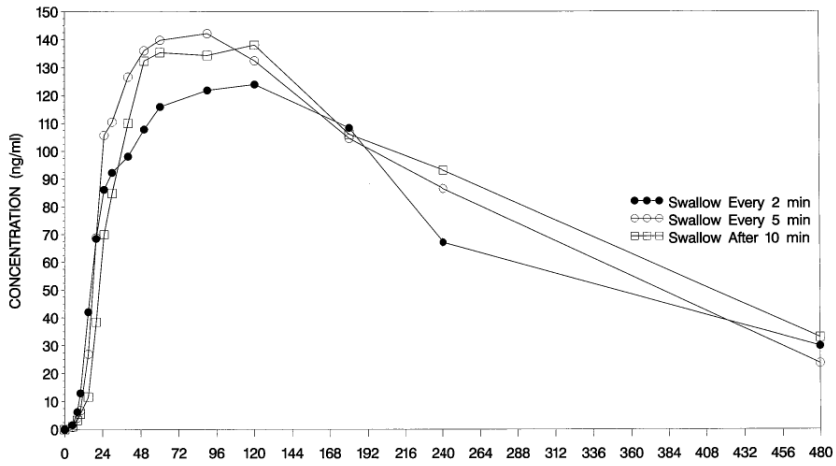
* Comparison was detected as statistically significant by ANOVA (α=0.05).

Summary of statistical comparisons of zolpidem results for (b) (4) 10 mg zolpidem powdered transmucosal tablets dosed by swallowing every 5 minutes (5-Min) and dosed by swallowing once at 10 minutes (10-Min) when administered as a single 10 mg dose after an overnight fast to 8 subjects.

Parameter	Least-Squares Means [1] 5-Min	10-Min	Ratio [2]	Power [3]	90% Confidence Interval [4] Lower	Upper
AUC 0-t (ng-min/ml)	39591	40921	0.967	0.61	0.822	1.113
Cmax (ng/ml)	168	172	0.977	0.68	0.843	1.112
Tmax (minutes)	76.6	66.9	1.146	0.09	-	-
Ln-Transformed:						
AUC 0-t (ng-min/ml)	36737	39408	0.932	0.68	0.802	1.083
Cmax (ng/ml)	162	167	0.970	0.67	0.832	1.130

1. Least-squares geometric means for ln-transformed data.
2. Ratio calculated as 5-Min least-squares mean divided by the 10-Min least-squares mean. None of the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the 10-Min mean or a ratio of 1.25 (ln-transformed results).
4. Confidence interval on the ratio.

Least-square mean zolpidem plasma concentration time profile (n=8)



Conclusions

- The pharmacokinetic results of treatment 2 (swallowing every 5 minutes) are comparable to those obtained from treatment 3 (swallowing once after 10 minutes)

- From the mean PK profile the extent of absorption from swallowing every 2 minutes appears to be less than that from swallowing once after 10 minutes and, also less than that from swallowing every 5 minutes.

ZI-04-002-002: Single-Dose 3-Way Fixed-Sequence Pilot Fasted Bioavailability Study of Zolpidem 10 mg (10-minute Dissolution Time) Tablets in Healthy Volunteers

Objectives:

The objectives of this study were to compare the pharmacokinetics of a zolpidem formulation with that of Ambien®, and to compare the effect of saliva swallowing regimens on the pharmacokinetics of the above zolpidem formulation after administration of single doses to normal healthy subjects under fasted conditions.

Study Design	This was a single-dose, 3-way fixed-sequence pilot bioequivalence study
Study Population	Healthy male and female Mean Age: 29 (20 to 37) years 8 subjects (2 males and 6 females)
Treatment Groups	Treatment A = Zolpidem tartrate 10 mg transmucosal tablet (Saliva Swallowed Every 2 Minutes) Treatment B = Zolpidem tartrate 10 mg transmucosal tablet (Saliva Swallowed Every 5 Minutes) Treatment C = Ambien® 10 mg tablet

Test and Reference products and Treatment Instructions	The test product was a single dose of one zolpidem 10 mg tablet administered sublingually with saliva swallowed every 2 minutes over 10 minutes and with saliva swallowed every 5 minutes over 10 minutes. The reference product was a single dose of one Ambien® 10 mg tablet, administered orally with 180 mL water.
Blood Sampling	Ten (10) mL blood samples were collected during each study period at Hour 0 (predose), and at 0.08, 0.17, 0.25, 0.33, 0.42, 0.5, 0.67, 0.83, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0 and 12.0 hours postdose. A total of 48 blood samples (480 mL) per subject were drawn during the study for drug analysis.
Urine	None
Feces	None
PK Assessments	$AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, Tmax and $T_{1/2}$ of zolpidem were evaluated using noncompartmental methods. Bioequivalence between zolpidem transmucosal (10 minute dissolution time) and Ambien® 10 mg tablets was evaluated by comparing the mean ratios and 90% confidence intervals (CI) of Cmax, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ for zolpidem transmucosal tablet with saliva swallowed every 2 minutes over 10 minutes (Treatment A) vs. Ambien® 10 mg tablets (Treatment C), and for zolpidem transmucosal tablet with saliva swallowed every 5 minutes over 10 minutes (Treatment B) vs. Treatment C. The effect of saliva swallowing rate on the pharmacokinetics of the test formulation was evaluated by performing mean concentration by time comparisons, by comparing the mean ratios of Cmax and AUC prior to and after natural log transformation, and by comparing median Tmax for Treatment A vs. Treatment B.
PD Assessments	None
Statistical Methods	Descriptive statistics, including arithmetic mean, sample size (N), standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV), median, minimum (min), and maximum (max), were computed for concentrations and each derived pharmacokinetic parameter by treatment. Descriptive statistics for ln-transformed Cmax, AUC(0-t), AUC(0-inf), and for zolpidem were also provided for each treatment. The pharmacokinetic parameter estimates were evaluated by Analysis of Variance (ANOVA) using the General Linear Models procedures of SAS® Version 8.2, with subject and treatment as variables. The SAS® estimate statement was used to obtain estimates of the adjusted differences between treatment means and the associated standard errors of the differences. The 90% confidence intervals (CI) for the difference between treatment least-squares means (LSMs) were derived from ANOVA on pharmacokinetic parameters Cmax and

	AUC prior to and after the natural log transformation. The percent mean ratios of each test treatment were computed with respect to the reference treatment.

RESULTS:

The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments A and C

	Plasma Zolpidem					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	238	56.3	239	62.3	80.20 - 119.17	99.7
Tmax(hr)	1.53	0.999	0.990	0.508	. - .	.
AUC(0-t)(ng*hr/mL)	969.6	218.2	874.1	240.1	95.88 - 125.96	110.9
AUC(0-inf)(ng*hr/mL)	1000	237.5	910.1	265.8	94.37 - 125.48	109.9
T1/2(hr)	2.10	0.329	2.17	0.481	. - .	.
Kel(1/hr)	0.336	0.0439	0.332	0.0648	. - .	.
AUCR	0.972	0.0198	0.966	0.0327	. - .	.
ln(Cmax)	5.449	0.2269	5.438	0.3056	82.47 - 123.82	101.1
ln[AUC(0-t)]	6.851	0.2537	6.734	0.3126	94.59 - 133.45	112.4
ln[AUC(0-inf)]	6.880	0.2659	6.770	0.3321	93.15 - 133.74	111.6

Treatment A = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 2 Minutes): Test
Treatment C = 1 x 10 mg Ambien® Tablet: Reference

The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments B and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments B and C

	Plasma Zolpidem					
	Treatment B		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	232	58.5	239	62.3	77.69 - 116.66	97.2
Tmax(hr)	0.960	0.442	0.990	0.508	. - .	.
AUC(0-t)(ng*hr/mL)	961.4	234.6	874.1	240.1	94.94 - 125.02	110.0
AUC(0-inf)(ng*hr/mL)	1003	261.2	910.1	265.8	94.66 - 125.78	110.2
T1/2(hr)	2.30	0.510	2.17	0.481	. - .	.
Kel(1/hr)	0.314	0.0661	0.332	0.0648	. - .	.
AUCR	0.963	0.0267	0.966	0.0327	. - .	.
ln(Cmax)	5.420	0.2398	5.438	0.3056	80.17 - 120.37	98.2
ln[AUC(0-t)]	6.837	0.2791	6.734	0.3126	93.30 - 131.64	110.8
ln[AUC(0-inf)]	6.876	0.2974	6.770	0.3321	92.77 - 133.19	111.2

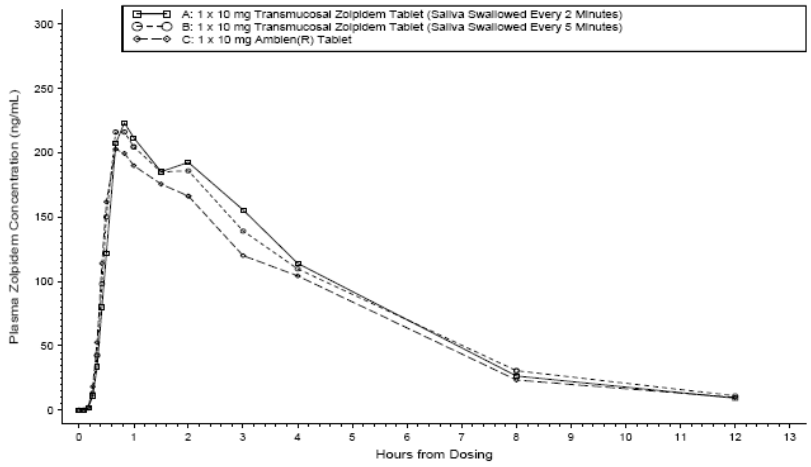
Treatment B = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 5 Minutes): Test
Treatment C = 1 x 10 mg Ambien® Tablet: Reference

The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and B are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments A and B

	Plasma Zolpidem					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	238	56.3	232	58.5	82.53 - 122.64	102.6
Tmax(hr)	1.53	0.999	0.960	0.442	. - .	.
AUC(0-t)(ng*hr/mL)	969.6	218.2	961.4	234.6	87.18 - 114.53	100.9
AUC(0-inf)(ng*hr/mL)	1000	237.5	1003	261.2	85.62 - 113.85	99.7
T1/2(hr)	2.10	0.329	2.30	0.510	. - .	.
Kel(1/hr)	0.336	0.0439	0.314	0.0661	. - .	.
AUCR	0.972	0.0198	0.963	0.0267	. - .	.
ln(Cmax)	5.449	0.2269	5.420	0.2398	83.95 - 126.05	102.9
ln[AUC(0-t)]	6.851	0.2537	6.837	0.2791	85.35 - 120.42	101.4
ln[AUC(0-inf)]	6.880	0.2659	6.876	0.2974	83.80 - 120.31	100.4
Treatment A = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 2 Minutes): Test Treatment B = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 5 Minutes): Reference						

Mean Plasma Zolpidem Concentrations Versus Time



Conclusions

- The pharmacokinetic results show that the treatment A (swallowing every 2 minutes) and treatment C (swallowing every 5 minutes) were not bioequivalent to reference Ambien®.

- From the mean PK profile the extent of absorption appeared to be similar for all the treatments. However, AUC for Ambien® treatment group appeared to be slightly lower than sublingual zolpidem treatments.

Note: This study used 10 mg sublingual tablet, which is not the final formulation strength.

ZI-04-003-003: Single-Dose 3-Way Fixed-Sequence Pilot Fasted Bioavailability Study of Zolpidem 10 mg (5-Minute Dissolution Time) Tablets in Healthy Volunteers

Objectives:

The objective of this study was to compare the pharmacokinetics of a zolpidem formulation with that of Ambien®, and to compare the effect of saliva swallowing regimens on the pharmacokinetics of the above zolpidem formulation after administration of single doses to normal healthy subjects under fasted conditions.

Study Design	This was a single-dose, 3-way fixed-sequence pilot bioavailability study
Study Population	Healthy male and female Mean Age: 25 (20 to 30) years 8 subjects (2 males and 6 females)
Treatment Groups	Treatment A = Zolpidem tartrate 10 mg transmucosal tablet (Saliva Swallowed Every 2 Minutes) Treatment B = Zolpidem tartrate 10 mg transmucosal tablet (Saliva Swallowed Every 5 Minutes) Treatment C = Ambien® 10 mg tablet
Test, Reference products and Treatment Instructions	The test product was a single dose of one zolpidem 10 mg tablet administered sublingually with saliva swallowed every 2 minutes over 10 minutes and with saliva swallowed every 5 minutes over 10 minutes. The reference product was a single dose of one Ambien® 10 mg tablet, administered orally with 180 mL water.
Blood Sampling	Ten (10) mL blood samples were collected during each study period at Hour 0 (predose), and at 0.08, 0.17, 0.25, 0.33, 0.42, 0.5, 0.67, 0.83, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0 and 12.0 hours postdose. A total of 48 blood samples (480 mL) per subject were drawn during the study for drug analysis.
Urine	None
Feces	None
PK Assessments	AUC_{0-t}, AUC_{0-inf}, C_{max}, Tmax and $T_{1/2}$ of zolpidem were evaluated using noncompartmental methods. Bioequivalence between zolpidem

	transmucosal (5-minute dissolution time) and Ambien® 10 mg tablets was evaluated by comparing the mean ratios and 90% confidence intervals (CI) of Cmax and AUC [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$] for zolpidem transmucosal tablet with saliva swallowed every 2 minutes over 10 minutes (Treatment A) versus Ambien® 10 mg tablets (Treatment C), and for zolpidem transmucosal tablet with saliva swallowed every 5 minutes over 10 minutes (Treatment B) versus Treatment C. The effect of saliva swallowing rates on the pharmacokinetics of the test formulation was evaluated by performing mean concentration by time comparisons, and by comparing the mean ratios of Cmax and AUC prior to and after natural log-transformation, and of Tmax for Treatment A versus Treatment B. Additional post hoc analyses were performed on Cmax, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ on subsets of subjects, and on partial AUCs from all subjects and following exclusion of Subjects 1 and 2. Plasma zolpidem partial AUCs [$AUC_{(0-5\ min.)}$, $AUC_{(0-10\ min.)}$, $AUC_{(0-15\ min.)}$, $AUC_{(0-20\ min.)}$, $AUC_{(0-25\ min.)}$, and $AUC_{(0-30\ min.)}$] were calculated.
PD Assessments	None
Statistical Methods	Descriptive statistics, including arithmetic mean, sample size (N), standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV), median, minimum (min), and maximum (max), were computed for concentrations and each derived pharmacokinetic parameter by treatment. Descriptive statistics for natural log-transformed $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} for zolpidem were also provided for each treatment. The pharmacokinetic parameter estimates were evaluated by Analysis of Variance (ANOVA), with subject and treatment as variables. The 90% CI for the difference between treatment least-squares means (LSMs) were derived from ANOVA on pharmacokinetic parameters Cmax and AUC prior to and after the natural log-transformation. The percent mean ratios of each test treatment were computed with respect to the reference treatment.

RESULTS:

The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments A and C

Pharmacokinetic Parameters	Plasma Zolpidem Treatment A Arithmetic Mean	Treatment A SD	Treatment C Arithmetic Mean	Treatment C SD	90% CI	% Mean Ratio
Cmax(ng/mL)	232	61.0	233	30.3	85.51 - 113.31	99.4
Tmax(hr)	0.883	0.500	1.00	0.827	. - .	.
AUC(0-t)(ng*hr/mL)	941.5	197.1	759.9	240.4	107.24 - 140.54	123.9
AUC(0-inf)(ng*hr/mL)	986.4	230.5	791.7	271.0	105.61 - 143.57	124.6
T1/2(hr)	2.42	0.550	2.25	0.592	. - .	.
Kel(1/hr)	0.298	0.0602	0.326	0.0806	. - .	.
AUCR	0.959	0.0287	0.967	0.0271	. - .	.
ln(Cmax)	5.417	0.2541	5.445	0.1298	84.99 - 111.39	97.3
ln[AUC(0-t)]	6.828	0.2125	6.591	0.3076	109.01 - 147.21	126.7
ln[AUC(0-inf)]	6.870	0.2347	6.626	0.3314	108.41 - 150.42	127.7

Treatment A = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 2 Minutes): Test
Treatment C = 1 x 10 mg Ambien(R) Tablet: Reference

The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments B and C are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments B and C

Pharmacokinetic Parameters	Plasma Zolpidem Treatment B Arithmetic Mean	Treatment B SD	Treatment C Arithmetic Mean	Treatment C SD	90% CI	% Mean Ratio
Cmax(ng/mL)	222	29.8	233	30.3	81.22 - 109.02	95.1
Tmax(hr)	0.632	0.131	1.00	0.827	. - .	.
AUC(0-t)(ng*hr/mL)	812.0	252.7	759.9	240.4	90.20 - 123.50	106.9
AUC(0-inf)(ng*hr/mL)	857.4	317.6	791.7	271.0	89.31 - 127.28	108.3
T1/2(hr)	2.32	0.826	2.25	0.592	. - .	.
Kel(1/hr)	0.321	0.0758	0.326	0.0806	. - .	.
AUCR	0.961	0.0499	0.967	0.0271	. - .	.
ln(Cmax)	5.394	0.1332	5.445	0.1298	83.05 - 108.85	95.1
ln[AUC(0-t)]	6.656	0.3164	6.591	0.3076	91.84 - 124.02	106.7
ln[AUC(0-inf)]	6.697	0.3582	6.626	0.3314	91.19 - 126.52	107.4

Treatment B = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 5 Minutes): Test
Treatment C = 1 x 10 mg Ambien(R) Tablet: Reference

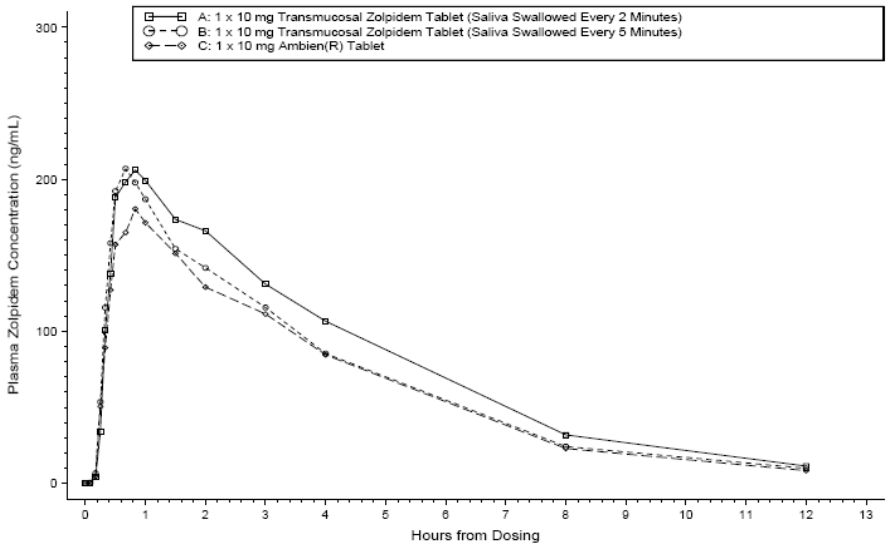
The arithmetic means and standard deviations of plasma zolpidem pharmacokinetic parameters and statistical comparisons of untransformed and ln-transformed Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and B are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Zolpidem for Treatments A and B

	Plasma Zolpidem					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax(ng/mL)	232	61.0	222	29.8	89.90 - 119.12	104.5
Tmax(hr)	0.883	0.500	0.632	0.131	. - .	.
AUC(0-t)(ng*hr/mL)	941.5	197.1	812.0	252.7	100.36 - 131.53	115.9
AUC(0-inf)(ng*hr/mL)	986.4	230.5	857.4	317.6	97.52 - 132.57	115.0
T1/2(hr)	2.42	0.550	2.32	0.826	. - .	.
Kel(1/hr)	0.298	0.0602	0.321	0.0758	. - .	.
AUCR	0.959	0.0287	0.961	0.0499	. - .	.
ln(Cmax)	5.417	0.2541	5.394	0.1332	89.39 - 117.16	102.3
ln[AUC(0-t)]	6.828	0.2125	6.656	0.3164	102.15 - 137.94	118.7
ln[AUC(0-inf)]	6.870	0.2347	6.697	0.3582	100.93 - 140.04	118.9

Treatment A = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 2 Minutes): Test
Treatment B = 1 x 10 mg Transmucosal Zolpidem Tablet (Saliva Swallowed Every 5 Minutes): Reference

Mean Plasma Zolpidem Concentrations Versus Time



Conclusions

- Treatment A (swallowing every 2 minutes) and treatment C (swallowing every 5 minutes) were not bioequivalent to reference Ambien®.

- The extent of absorption was approximately 20% higher for treatment A (swallowing every 2 minutes). The AUC for Ambien treatment group appeared to be lower than sublingual zolpidem treatments.

Note: This study used 10 mg sublingual tablet, which is not the final formulation strength.

B OCP Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics *NEW DRUG APPLICATION FILING AND REVIEW FORM*			
(1) General Information About the Submission			
	Information		Information
NDA Number	**22328**	**Brand Name**	**Intermezzo®**
OCPB Division (I, II, III)	**DCP-1**	**Generic Name**	**Zolpidem Tartrate**
Medical Division	**HFD-120**	**Drug Class**	**Imidazole Pyridine Sedative/Hypnotic**
OCPB Reviewer	**Jagan Mohan Parepally**	**Indication(s)**	**Treatment of Insomnia**
OCPB Team Leader	**Veneeta Tandon**	**Dosage Form**	**Sublingual Tablet**
Date of Submission	**09/30/2008**	**Dosing Regimen**	**As-needed after awakening in the middle of the night**
Estimated Due Date of OCP Review	**6/12/2009**	**Route of Administration**	**Oral**
PDUFA Due Date	**7/31/2009**	**Sponsor**	**Transcept Pharma Inc.**

b) Division Due Date	**6/29/2009**	**Priority Classification**	**S**

(a) Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of Intermezzo® (Zolpidem tartrate sublingual tablet) with Ambien® (NDA 19-908) as the reference listed drug.

Intermezzo® is a sublingual tablet formulation of zolpidem tartrate. The sponsor has developed a low-dose zolpidem tartrate sublingual tablet, 1.75 mg and 3.5 mg, for the as-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN). The 3.5 mg dose of the zolpidem tartrate sublingual tablet is the recommended dose for patients older than 18 years but less than 65 years of age, whereas the 1.75 mg dose is the recommended dose for patients older than 65 years and patients with compromised hepatic function. The adult dose of Ambien® for treatment of insomnia is 10 mg and 5 mg for elderly and hepatically impaired patients.

The clinical data package in this NDA includes a total of 12 studies. Four studies were exploratory in nature, utilized prototype formulations and were completed prior to the filing of an IND. Subsequent studies were conducted under IND 69,209. Clinical safety and efficacy of the zolpidem tartrate sublingual tablet is supported by 2 well-controlled studies that provide evidence of efficacy for the intended claim. The NDA also includes studies specifically requested by the Agency to address food effect, relative bioavailability (versus the reference-listed drug, Ambien®), and determine the pharmacodynamic (PD) effects of immediate swallowing Vs delayed swallowing of the tablet.

The two dosage strengths of sublingual tablets are [redacted] (b) (4). Based on the limits of the 90% CI of the mean treatment of ratio of the PK parameters (Cmax and AUC0-t, 0-inf) were contained within the predetermined interval of 0.8 to 1.25.

Pharmacokinetic Studies

ZI-15 is pivotal bioequivalence study comparing single dose pharmacokinetics of 3.5 mg sublingual zolpidem tablet with 10 mg ambient tablet and also includes effect of food on the absorption of zolpidem.
ZI-13 is a formulation bridging study comparing the bioequivalence of IND formulation with commercial formulation used in pivotal BE study.
ZI-14 is a pharmacokinetic study comparing 1.75 and 3.5 mg tablet in healthy elderly subjects with healthy non-elderly subjects.

Pharmacodynamic Studies:
Studies include
Study ZI-05-009: In this study PK/PD, safety and dose proportionality of 3 doses (1.00, 1.75 and 3.5 mg) of zolpidem tartrate sublingual tablet vs. placebo were evaluated.
ZI-16: In this study comparative PD effects and late PK effects of sublingual vs. oral zolpidem tartrate sublingual tablet dosing were evaluated.
ZI-17: In this study comparative early PK/PD parameters between sublingual vs. oral dosing, dose proportionality were evaluated.

Efficacy Studies
ZI-06-010: Efficacy and safety of 2 (1.75 and 3.5 mg) doses of zolpidem tartrate sublingual tablet vs. placebo in a sleep lab with scheduled awakening in adult patients with insomnia characterized by difficulty returning to sleep after MOTN awakening.

ZI-12: Efficacy and safety of zolpidem tartrate sublingual tablet vs. placebo; (subjective measures) in an out-patient setting with as needed dosing over 28 days in adult patients with insomnia characterized by difficulty returning to sleep after MOTN awakening.

Pilot Studies:
These studies were conducted before initiation of IND. Studies include ZI-04-001-001, ZI-04-002-002, ZI-04-003-003, ZI-04-007. In all the above studies higher doses (10 mg) of zolpidem were used.

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

Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 1:	**X**	**3**	**3**	Study ZI-05-009, ZI-16 and ZI-17
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -	**X**	**4**	**4**	Pilot Studies conducted before IND
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		**3**	3	Study ZI-13, ZI-14 and ZI-15 Studies also include 1) Bridging study for IND and commercial formulation (ZI-13) 2) Food-drug interaction (ZI-15) 3) Evaluation of PK profile in geriatric population (ZI-14)
replicate design; single / multi dose:				
Food-drug interaction studies:		-		Study ZI-15
Dissolution:	-	-	-	
(IVIVC):				
Bio-waiver request based on BCS	-	-	-	
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References		-	-	
Total Number of Studies		**11**	**11**	

(c) Filability and QBR comments				
b)	**"X" if yes**			
Application filable?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?				
QBR questions (key issues to be considered)	Is BE shown between sublingual tablet and reference Ambien tablets Is final commercial product bioequivalent to IND formulation used? Is there a dose proportionality between 1.75 and 3.5 mg tablets? Is there a food-effect on zolpidem sublingual tablet formulation?			
Other comments or information not included above	None			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22328 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Veneeta Tandon, Ramana Uppoor, Mehul Mehta)

Table 1: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	ZI-04-001-001	Section 5.3.1.1.1	Determine PK profiles of powdered zolpidem tartrate 10 mg lozenge after administration of single doses, using different swallowing times	3-way,fixed sequence, single dose, pilot study	Powdered zolpidem tartrate sublingual lozenge,[a] 10 mg; sublingual	8	Healthy Subjects	Single dose	Complete; full
BA	ZI-04-002-002	Section 5.3.1.1.2	Compare PK of a zolpidem formulation vs. Ambien®, and determine effect of saliva swallowing regimens on PK of zolpidem formulations (10-min dissolution time)	3-way,fixed sequence, single dose, pilot study	Zolpidem tartrate sublingual lozenge,[a] 10 mg; sublingual Ambien®, 10 mg tablet; oral	8	Healthy Subjects	Single dose	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	ZI-15	Section 5.3.3.1.3	Evaluate effect of food on PK plus comparative PK for zolpidem tartrate sublingual lozenge vs. Ambien® 10 mg	Randomized, open-label, 3-period, 6-sequence crossover	Zolpidem tartrate sublingual lozenge, 3.5 mg (fed); sublingual Zolpidem tartrate sublingual lozenge, 3.5 mg (fasted); sublingual Ambien®, 10 mg tablet (fasted); oral	36	Healthy Subjects	Single dose	Complete; full
PK/PD	ZI-05-009	Section 5.3.4.1.1	Evaluate PK/PD, safety and dose proportionality of 3 doses of zolpidem tartrate sublingual lozenge vs. placebo	Randomized, double-blind, daytime, placebo-controlled, 4-way crossover	Zolpidem tartrate sublingual lozenge, 1.0, 1.75 and 3.5 mg; sublingual Placebo lozenge; sublingual	24	Healthy Subjects	Single doses given on 2 consecutive days	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PD	ZI-16	Section 5.3.4.1.2	Evaluate comparative PD effects and late PK effects of sublingual vs. oral zolpidem tartrate sublingual lozenge dosing	Randomized, double-blind, 3-period, 6-sequence crossover	Zolpidem tartrate sublingual lozenge, 3.5 mg; oral Zolpidem tartrate sublingual lozenge, 3.5 mg ; held under tongue for 2 min Placebo; sublingual or oral	30	Healthy Subjects	Single dose	Complete; full
Efficacy and Safety	ZI-06-010	Section 5.3.5.1.1	Efficacy and safety of 2 doses of zolpidem tartrate sublingual lozenge vs. placebo in a sleep lab with scheduled awakening (objective and subjective measures)	Randomized, double-blind, placebo-controlled 3-way crossover	Zolpidem tartrate sublingual lozenge, 1.75 and 3.5 mg; sublingual Placebo lozenge; sublingual	82	Adult patients with insomnia characterized by difficulty returning to sleep after MOTN awakening	Single doses given on 2 consecutive nights	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	ZI-12	Section 5.3.5.1.2	Efficacy and safety of zolpidem tartrate sublingual lozenge vs. placebo; (subjective measures) in an out-patient setting with as needed dosing over 28 days	Randomized, double-blind, parallel group, placebo-controlled	Zolpidem tartrate sublingual lozenge, 3.5 mg; sublingual Placebo lozenge; sublingual	295 (150 active, 145 placebo)	Adult patients with insomnia characterized by difficulty returning to sleep after MOTN awakening	4 weeks *prn* dosing	Complete; full
PK/PD	ZI-17	Section 5.3.5.4.2	Evaluate comparative early PK/PD parameters between sublingual vs. oral dosing	Part I: Randomized, DB, double-dummy, placebo-controlled 3-way, 6-sequence crossover Part II: Randomized, open-label, single dose	Part I: Zolpidem tartrate sublingual lozenge, 3.5 mg; sublingual Zolpidem tartrate, 3.5 mg tablet; oral Placebo; sublingual or oral Part II: Ambien®, 10 mg tablet; oral	36	Healthy Subjects	Single dose	Complete; full

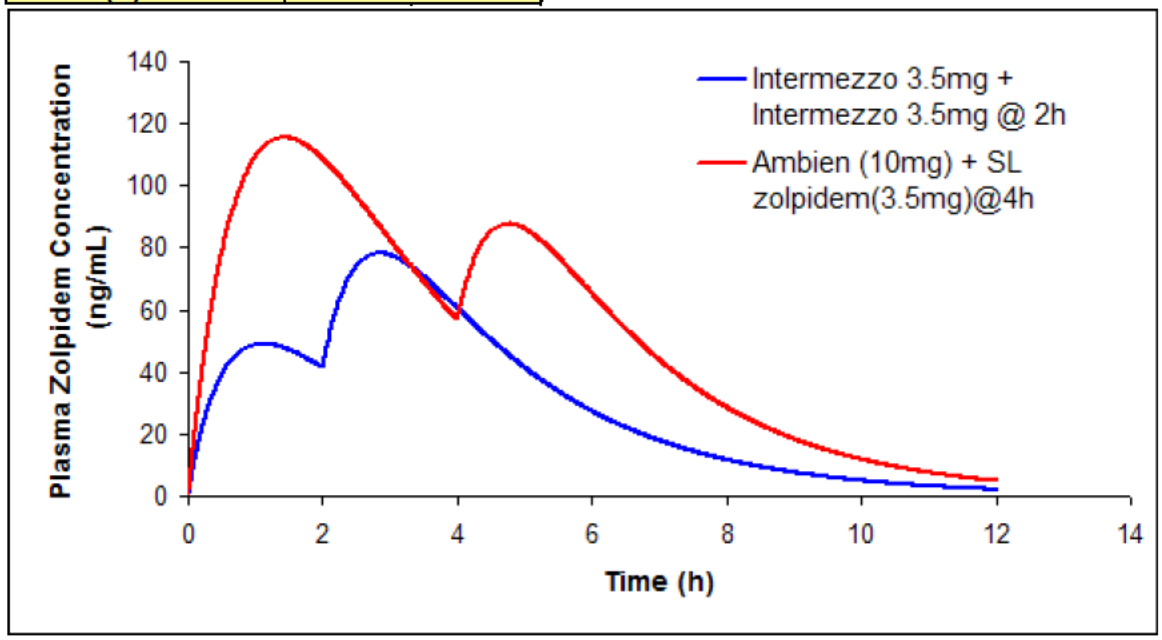
BA = bioavailability; BE = bioequivalence; DB = double-blind; MOTN = middle of the night; PK = pharmacokinetic; PD = pharmacodynamic

[a] "Tablet" is indicated as the dosage form in the clinical study protocol and report; the correct dosage form term is "lozenge".

B Pharmacokinetic Simulations to Assess The Effect of Potential Re-Dosing

INPUT		
D1 [mg]	10	3.5
Vd_F1 (L)	0.0434	0.0442
ka1 (L/h)	0.9737	1.6222
ke1	0.4836	0.4297
DosingTime(h)	4	2
D2 [mg]	3.5	3.5
Vd_F2 (L)	0.0442	0.0442
ka2 (L/h)	1.6222	1.6222
ke2	0.4297	0.4297
Ob. T(h)	12	

$$Cp = \frac{f * D * k_a}{V_d(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)$$



time(h)	Conc1(ng/mL)	Conc2(ng/mL)
0	0	0
0.0075	1.673491779	0.956029184
0.015	3.328748221	1.897421226
0.0225	4.965923945	2.824363029
0.03	6.585172363	3.7370392
0.0375	8.186645695	4.635632087
0.045	9.770494973	5.520321796
0.0525	11.33687005	6.391286227
0.06	12.88591962	7.248701096
0.0675	14.41779119	8.092739963
0.075	15.93263116	8.923574257
0.0825	17.43058474	9.741373305
0.09	18.91179604	10.54630435
0.0975	20.37640804	11.3385326
0.105	21.82456258	12.1182212
0.1125	23.25640042	12.88553132
0.12	24.67206121	13.64062214
0.1275	26.0716835	14.3836509
0.135	27.45540475	15.11477287
0.1425	28.82336138	15.83414145
0.15	30.17568871	16.54190815
0.1575	31.512521	17.23822259
0.165	32.83399149	17.92323258
0.1725	34.14023233	18.5970841

0.18	35.43137468	19.25992134
0.1875	36.70754865	19.91188671
0.195	37.96888332	20.55312087
0.2025	39.21550678	21.18376275
0.21	40.44754609	21.80394958
0.2175	41.66512735	22.41381689
0.225	42.86837564	23.01349854
0.2325	44.05741505	23.60312674
0.24	45.23236874	24.18283209
0.2475	46.39335884	24.75274357
0.255	47.54050658	25.31298857
0.2625	48.67393221	25.86369291
0.27	49.79375502	26.40498086
0.2775	50.90009338	26.93697517
0.285	51.99306473	27.45979706
0.2925	53.07278559	27.97356626
0.3	54.13937153	28.47840104
0.3075	55.19293725	28.97441818
0.315	56.23359652	29.46173306
0.3225	57.26146223	29.9404596
0.33	58.27664637	30.41071033
0.3375	59.27926005	30.8725964
0.345	60.2694135	31.32622758
0.3525	61.24721608	31.77171226
0.36	62.21277629	32.20915754
0.3675	63.16620178	32.63866917
0.375	64.10759933	33.06035159
0.3825	65.03707489	33.47430795
0.39	65.95473357	33.88064014

0.3975	66.86067965	34.27944878
0.405	67.75501659	34.67083325
0.4125	68.63784702	35.0548917
0.42	69.50927275	35.43172106
0.4275	70.36939482	35.80141707
0.435	71.21831343	36.16407428
0.4425	72.056128	36.51978607
0.45	72.88293716	36.86864468
0.4575	73.69883878	37.21074117
0.465	74.50392992	37.54616552
0.4725	75.29830688	37.87500656
0.48	76.08206522	38.19735203
0.4875	76.85529969	38.51328859
0.495	77.61810435	38.82290182
0.5025	78.37057245	39.12627624
0.51	79.11279655	39.42349531
0.5175	79.84486845	39.71464148
0.525	80.56687922	39.99979617
0.5325	81.27891919	40.27903976
0.54	81.98107802	40.55245168
0.5475	82.6734446	40.82011033
0.555	83.35610714	41.08209317
0.5625	84.02915314	41.33847667
0.57	84.69266941	41.58933638
0.5775	85.34674206	41.83474689
0.585	85.99145651	42.07478187
0.5925	86.62689751	42.30951406
0.6	87.25314912	42.53901533
0.6075	87.87029474	42.76335661

0.615	88.47841709	42.98260799
0.6225	89.07759823	43.19683866
0.63	89.66791958	43.40611696
0.6375	90.24946189	43.61051038
0.645	90.82230528	43.81008556
0.6525	91.38652921	44.00490833
0.66	91.94221252	44.19504366
0.6675	92.4894334	44.38055576
0.675	93.02826943	44.56150801
0.6825	93.55879756	44.737963
0.69	94.08109413	44.90998254

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/s/

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