CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022328Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA (Complete Response)
Application Number(s)	022328
Priority or Standard	Class 1 Resubmission
Submit Date(s)	9/27/11
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PDUFA Goal Date	11/27/11
Division / Office	DNP / ODE1
Reviewer Name(s)	Christopher D Breder, MD PhD
Review Completion Date	25 Oct 2011
Established Name	Zolpidem tartrate lozenge
(Proposed) Trade Name	Intermezzo
Therapeutic Class	Sedative Hypnotic
Applicant	Transcept Pharmaceuticals
Formulation(s)	sublingual lozenge
Dosing Regimen	x 1 qMiddle of the Night (MOTN) PRN
Indication(s)	Treatment of insomnia following MOTN awakening
Intended Population(s)	Insomnia patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended.

1.2 Risk Benefit Assessment

A primary concern with the Sedative Hypnotic class is the potential for residual effects. The zolpidem products carry a risk of having elevated plasma levels in females. This Medical Officer believes the Sponsor has adequately mitigated these risks by lowering the female dose to 1.75 mg per dosing and by recommending not to dose with less than four hours of sleep time remaining.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This Medical Officer does not believe a REMS is needed for this application. I agree with the Sponsor's plan to issue a Medication Guide and Patient Instructions for Use that focus on the proper dosing and potential hazards of next-day sedation.

1.4 Recommendations for Postmarket Requirements and Commitments

A principle concern with this drug is whether patients will follow the dosing guidance, as dosing with insufficient sleep time remaining, may lead to high residual drug levels. The Division had communicated their desire for the Sponsor to conduct a form of actual use study in the second Complete Response cycle; however, both parties agreed that the data would be difficult to collect in the setting of a controlled clinical trial. This Medical Officer would like the Sponsor to conduct a study in the setting of the drug being marketed that would provide this information.

The Sponsor should conduct the necessary studies to comply with the PREA requirement (e.g., ages 6-17).

2 Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory Activity Related to Submission

NDA 23-238/S0036 for the use of Intermezzo® 1.75 and 3.5 mg for the treatment of insomnia following middle of the night (MOTN) awakening was submitted 9/30/08. The Sponsor received two Complete Responses (CRs), 28 Oct 2009 and 14 JUL 2011. In the action letter for the second CR, the Division of Neurology Products (DNP) had

several concerns related to characterization of the pharmacokinetics and to the potential morning plasma levels of zolpidem:

- *a necessary first step in addressing DNP's concerns about residual morning levels of zolpidem from Intermezzo would be a more thorough characterization of the distribution of blood levels that can occur the morning after dosing;*
- to address the concern that zolpidem levels were not safe, the Sponsor should…*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.);*
- *depending on the residual zolpidem levels that might result after mitigation strategies are implemented, it might be necessary for you to demonstrate, in an adequately powered study with demonstrated assay sensitivity, that the levels still present do not present an unacceptable risk of next-day impairment.*

In addition to these issues and potential mitigations, DNP noted that they had a concern about whether subjects would comply with dosing instructions, possibly taking the drug with less than 4 hours of sleep time remaining. The Sponsor asserted that obtaining an accurate assessment of this compliance would be difficult in a controlled trial setting. DNP agreed, since even in a controlled environment (e.g., Study Z-12), deviations were noted. In lieu of the requested actual use study, DNP commented that it would be reasonable to estimate that patients would take this drug with 3 or 3.5 hours left to sleep and that this consideration should be taken into account when interpreting and assigning meaning to results of safety studies (e.g., Z-18, the "Driving Study") or pharmacokinetic studies (e.g., ZI-05-009).

A Type C meeting was held 16 September based on materials supplied by the Sponsor on 23 AUG 2011 and 07 SEP 2011. The primary focal points of the meeting were discussions of:

- the Sponsor's proposal to lower the recommended dose for females to 1.75 mg, since there was a gender effect giving rise to plasma levels approximately 40% higher in this population;
- (b) (4)
- the characterization of pharmacokinetics, and particularly, the variability and levels present in African –American subjects.

DNP and the Sponsor agreed that the Complete Response should focus on these issues.

The Sponsor's Complete Response submission of 27 SEP 2011 contains:

- An II-page summary of evidence supporting Transcept's proposal for dosing recommendations in males and females, (b) (4)

- Analysis datasets for subgroup analyses supporting the resubmission. (Section 5.3.5.3)

- Updates to labeling components for consistency with revised dosing recommendations and instructions.

    - Package Insert, Medication Guide, and Patient Instructions for Use (Section 1.14.1.3)
    - Annotated Package Insert, Medication Guide, and Patient Instructions for Use (Section 1.14.1.2)
    - Carton and container labels (Section 1.14.1.1)
    - Updated files for the proposed labeling in Structured Product Labeling (SPL) format.

This review focused on these materials, study reports by the Sponsor, as well as prior reviews by the DNP including:

- Complete Response Action letter of 14 JUL 2011
- DNP Director Memos of 14 JUL 2011 and 26 OCT 2009
- Cross Discipline Team Leader (CDTL) Memos of 03 SEP 2009 and 20 JUL 2011
- Medical Reviewer's Clinical Reviews of 03 SEP 2009 and 12 JUL 2011
- Statistical Review and Evaluations of 19 JUN 2009 and 08 JUL 2011
- Clinical Study Reports submitted by the Sponsor
    - ZI-06-10 A Randomized, Double-blind, Placebo-controlled, Crossover Study of the Efficacy and Safety of Sublingual zolpidem tartrate lozenge in Adult Patients with Insomnia Characterized by Difficulty Returning to Sleep after Middle-of the-Night (MOTN) Awakening
    - ZI-12 A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study Of The Efficacy And Safety Of The Zolpidem Tartrate Sublingual Lozenge In Adult Subjects With Insomnia Characterized By Difficulty Returning To Sleep After Awakening In The Middle-Of-The-Night (MOTN)
    - ZI-18 Assessment of Next-Morning Driving Performance after Middle of the Night Administration of Zolpidem Tartrate Sublingual Tablet 3.5 mg in Healthy Adult Volunteers: Single-Center, Double-Blind, Randomized, Placebo-Controlled, Four-Way Crossover Study

2.5.1 Other Regulatory Activity

The Intermezzo (zolpidem tartrate) partial waiver/deferral plan was reviewed by the PeRC PREA Subcommittee on September 02, 2009. The Division recommended a partial wavier from 0 (b)(4) years because the disease/condition does not exist in children and a deferral from 6 (b)(4) years because the product is ready for approval in adults. The PeRC agreed with the Division to grant a partial waiver because the disease/condition does not exist in children age 0 (b)(4) years. The PeRC is requesting an application certification of deferred studies and the required dates prior to the Division taking an approval action.

3 Significant Issues Related to Other Review Disciplines

3.1. Pharmacokinetics

The principle focus of the pharmacokinetic analysis was the support of the mitigation strategy lowering female dosing to 1.75 mg.

Sponsor's Analysis: The pharmacokinetic data to support the Intermezzo 1.75 mg dose in females and 3.5 mg dose in males is derived from the PK PD (ZI-05-009) study. This study investigated the pharmacokinetics and pharmacodynamics of Intermezzo doses of 1.0, 1.75, and 3.5 mg in 11 females and 13 males.

Plasma levels were approximately 45% higher in females than males. Higher levels in females are mostly attributed to lower apparent clearance (**Table 1**). The lower clearance in females is not explained by body weight, since the difference is still evident after normalization for body weight. Intermezzo mean C_{max}, AUC, and the 3-, 4-, and 5-hour plasma levels changed linearly with dose in females and males in the study.

Table 1 Mean Intermezzo Pharmacokinetic Parameters after Single Dose of Intermezzo 3.5, 1.75, and 1.0 mg in Females and Males (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-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)
$t_{1/2}$ (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)
C_3 (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)
C_4 (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)
C_5 (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_{SL} (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)

C_{max}: Maximum measured plasma concentration
t_{max}: Time of maximum measured plasma concentration
AUC_{0-t}: The area under the plasma concentration-time curve from time 0 to the last measurable concentration
AUC_{0-inf}: The area under the plasma concentration versus time curve from time zero (0) to infinity
$t_{1/2}$: Apparent terminal elimination half-life
C_3: Plasma concentration at 3 hours post-dose
C_4: Plasma concentration at 4 hours post-dose
C_5: Plasma concentration at 5 hours post-dose
app CL_{SL}: apparent sublingual clearance

The 3-, 4-, and 5-hour plasma data from six Intermezzo pharmacokinetic studies was pooled by the sponsor to gain a better understanding of the distribution of zolpidem plasma levels at these time points (**Table 2**). The pooled data suggests that the average 4-hour plasma levels in females, following the 1.75 mg dose, are in a range similar to the 4-hour levels in males, following the 3.5 mg dose.

Table 2 Mean (SD) Plasma Concentration at 3, 4, and 5 hours in Females Following the 1.75 mg dose and in males Following the 3.5 mg Dose.

Plasma Concentration (ng/ml)	Intermezzo 1.75 mg	Intermezzo 3.5 mg
	Women (n =81)	Men (n = 96)
3 hours	19.82 (8.42)	26.20(9.82)
4 hours	16.32 (7.11)	20.62 (8.44)
5 hours	12.56 (6.75)	15.05 (7.74)

[a] data pooled from studies -009, -13, -14 (non-elderly cohort), -15, -16, and -17. For the -13, -14, -15, -16, and -17 studies, the 1.75 mg plasma levels in women were calculated by dividing the 3.5 mg levels by two.
Analysis datasets for subgroup analyses supplied in Section 5.3.5.3

The predictive probability of a subject being exposed to a high zolpidem blood level at 3, 4, and 5 hours following a dose of Intermezzo was also assessed. The analysis indicated that the predictive probability of Intermezzo 1.75 mg producing a plasma level of 40 ng/ml or higher in females at 3, 4, and 5 hours post-dose is lower than that of 10 mg zolpidem measured at 6 and 8 hours post-dose (**Table 3**).

Table 3 The Predictive Probabilities of Exceeding Threshold Plasma Concentration Values (female subjects)

Plasma concentrations (ng/ml)	Predictive probabilities Intermezzo 1.75 mg[a]			Predictive probabilities 10 mg oral zolpidem[b]	
	3 hour	4 hour	5 hour	6 hour	8 hour
10	0.875	0.810	0.646	0.964	0.898
20	0.492	0.304	0.138	0.872	0.685
30	0.116	0.030	0.006	0.676	0.377
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

[a] Based on data pooled from all studies (untransformed data). For the -13, -14, -15, -16, and -17 studies, the 1.75 mg plasma levels in women were calculated by dividing the 3.5 mg levels by two.
[b] Based on data pooled from studies -15 and -17 (untransformed data)

In males, 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 is similar to or lower than that of 10 mg zolpidem measured at 8 hours post-dose. The probabilities at other concentrations are shown in **Table 4**.

Table 4 Predictive Probabilities of Exceeding Threshold Plasma Concentration Values (male subjects)

Plasma concentrations (ng/ml)	Predictive probabilities Intermezzo 3.5 mg[a]			Predictive probabilities 10 mg oral zolpidem[b]	
	3 hour	4 hour	5 hour	6 hour	8 hour
10	0.946	0.891	0.741	0.820	0.679
20	0.733	0.529	0.263	0.632	0.422
30	0.351	0.137	0.029	0.405	0.196
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

[a] Based on data pooled from all studies (untransformed data)
[b] Based on data pooled from Studies 15 and 17 (untransformed data)

Covariate analysis of the pooled 3-, 4-, and 5-hour plasma levels in non-elderly females and nonelderly males indicated that age, body weight and race (African-Americans and non-African- Americans) did not significantly influence Intermezzo plasma levels (**Table 5**). The data pooled from all 3.5 mg Intermezzo pharmacokinetic studies suggests that mean C_{max}, and the 3-, 4-, and 5-hour plasma levels were similar among Caucasians, African-Americans and the subgroups.

Table 5 Mean (%CV) Intermezzo 3.5 mg Cmax and Plasma Levels at 3, 4, and 5 hours in males

	All[a] Men (n = 96)	African American Men (n = 35)	Caucasian Men (n = 58)	Other[b] 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)

[a] data pooled from studies -009, -13, -14 (non-elderly cohort), -15, -16, and -17.
[b] 3 subjects were listed as Asian.
Analysis datasets for subgroup analyses supplied in Section 5.3.5.3

Medical Reviewer's Analysis and Comments: The Sponsor has proposed lowering the dose in females to 1.75 mg to mitigate the concern of elevated zolpidem plasma levels. Each demonstration of the Sponsor's data (i.e., **Tables 1-5**) suggests that by lowering the females' dose to 1.75 mg, the probability of the more worrisome levels seen in the female 3.5 mg group is reduced. This is also demonstrated in the Medical Reviewer's analysis of the ZI-05-009 data set assessing zolpidem concentration

distribution by gender and dose (**Figure 4**). In this analysis, no female subjects at 3hr post-dose had levels greater than 40 ng/ml in the 1.75 mg group, while almost half had levels between 35 and 92 ng/ml in the 3.5 mg group. In summary, this Medical Reviewer believes the dose reduction in females mitigates the concern about the potential residual morning zolpidem levels.

Based on the data from **Table 5** this reviewer does not believe that the variance of the PK of African –American males is sufficiently different to warrant specific labeling.

4 Review of Efficacy

Efficacy Summary

This review will not reanalyze prior findings of efficacy but will highlight and independently verify the Sponsor's supporting statements for the use of 1.75 mg in female subjects.

4.1 Indication

Intermezzo® is to be indicated for the treatment of insomnia following MOTN awakening.

4.1.1 Methods

The efficacy support for Intermezzo 1.75 mg dose in females is 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 with a history of middle-of-the-night awakening. Latency to persistent sleep (LPS_{MOTN}) and Total Sleep Time (TST_{MOTN}) after a scheduled MOTN awakening were the primary and the principal secondary endpoints of the study.

4.1.2 Demographics

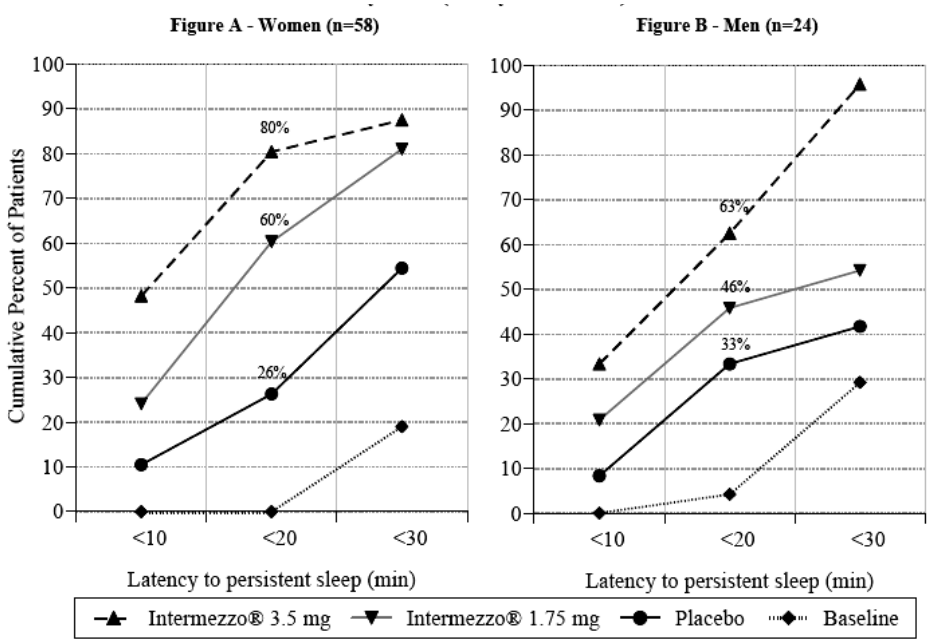
82 patients (58 female, 24 male) were randomized and analyzed for efficacy.

4.1.3 Analysis of Primary and Key Secondary Endpoint(s)

Sponsor's Analysis: Statistically significant improvements compared to placebo were observed in both genders at their respective doses of 1.75 mg for female patients and 3.5 mg for male patients.
• In females, LPS_{MOTN} was 15.70 min vs. placebo 27.73 min ($p<0.0001$); Sleep Onset Latency (SOL_{MOTN}) was 28.43 min vs. placebo 38.54 min ($p=0.0008$); TST_{MOTN} was 199.51 min vs. placebo 185.15 min ($p=0.0028$) and Subjective TST was 161.39 min vs. placebo 147.92 min ($p=0.0330$). All sleep variables are least square values.
• In males, LPS_{MOTN} was 12.74 min vs. placebo 29.03 min ($p<0.0001$); SOL_{MOTN} was

21.92 min vs. placebo 37.97 min (p=0.0001); TST_{MOTN} was 207.02 min vs. placebo 178.33 min (p<0.0001) and Subjective TST was 169.28 min vs. placebo 146.81 min (p=0.0422). All sleep variables are least square values.

Figure 1 Cumulative % of Patients Asleep (After MOTN Awakening) at Sequential 10-Minute Intervals by PSG (Study ZI-06-010)



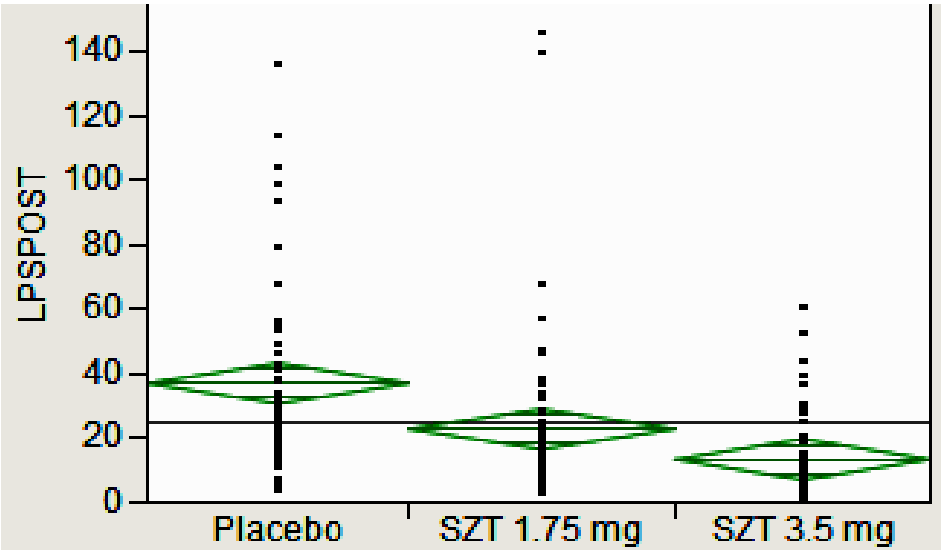
Analysis datasets for subgroup analyses supplied in Section 5.3.5.3

Medical Reviewer's Analysis and Comments: The Sponsor has adequately verified that 1.75 mg is efficacious in females for the claim of treating LPS for MOTN awakening. This is verified by the Medical Reviewer's independent analysis (**Figure 2**) In an ANOVA analysis of the LPS Post awakening in females, the 1.75 mg group mean was 23.1 min (90% CI:16.8, 29.3) and the Placebo arm was 37.2 min (90%CI:30.9, 43.5). The difference was statistically significant (P< 0.004) using Dunnett's test. The 1.75 mg dose in females appears to have a similar effect as the 3.5 mg dose in males (see **Figure 1)**. At each latency period, the responder rate appears to be with 10% of the other gender's rate.

4.1.4 Analysis of other Secondary Endpoints(s)

Medical Reviewer's Analysis and Comments: Parameters related to sleep maintenance, such as Wake (time) after Sleep Onset (WASO) and the Number of Awakenings (NAW) were analyzed for the 1.75 mg dose in Females using the identical methodology as described in Section 6.14. Neither endpoint (WASOPOST and NAWPOST) were significantly reduced relative to PBO in either the 3.5 or 1.75 mg dose groups. While this was not a specific claim of the Sponsor, the analysis was performed to more completely characterize the effects for females at 1.75 mg.

Figure 2 LPS Post MOTN Awakening in Females by Dose Group



Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Placebo	57	37.2281	3.1886	30.933	43.523
SZT 1.75 mg	58	23.0603	3.1610	16.820	29.301
SZT 3.5 mg	56	13.6384	3.2169	7.288	19.989

Std Error uses a pooled estimate of error variance

Comparisons with a control using Dunnett's Method

Control Group = Placebo

|d|	Alpha
2.23085	0.05

Level	Abs(Dif)-LSD	p-Value
Placebo	-10.1	1.0000
SZT 1.75 mg	4.152	0.0037*
SZT 3.5 mg	13.49	<.0001*

Positive values show pairs of means that are significantly different.

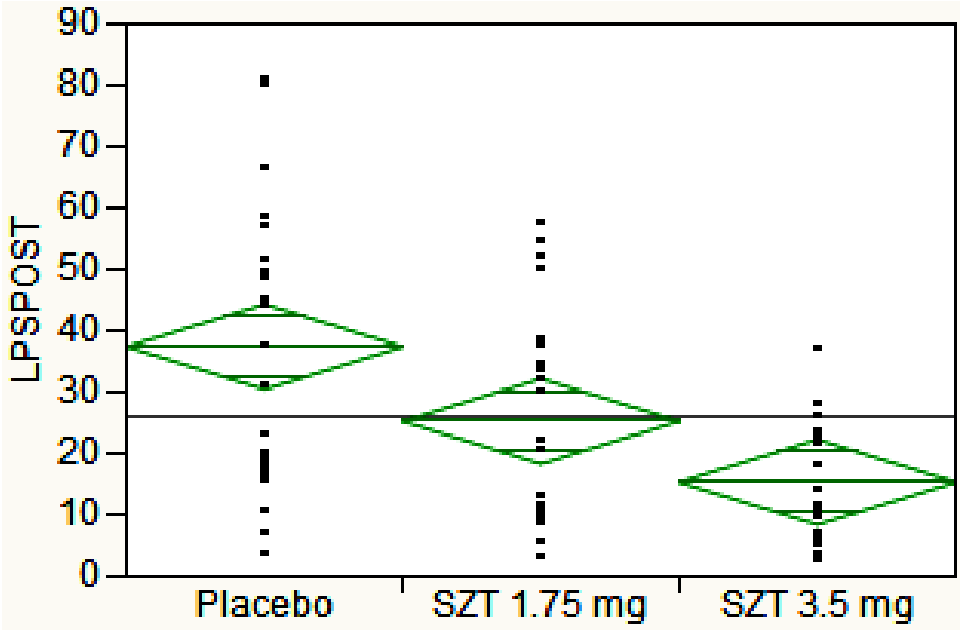
Figure Legend

This figure demonstrates the 95% confidence intervals (green diamonds) for the LPS (Y axis, in minutes) in females in the PBO, 1.75 mg, and 3.5 mg dose groups from the ZI-10 Study. The middle bar in each diamond represents the group mean. Individual data points are represented by the dots rising vertically in each dose group. The black horizontal line crossing through the 1.75 mg diamond represents the overall mean of the three groups. Descriptive statistics of dose group, N, mean standard error, and the 95% confidence limits. Statistical testing using the Dunnett's Test with the PBO groups as a control arm is presented in the bottom panel.

4.1.5 Other Endpoints

Medical Reviewer's Analysis and Comments: While the efficacy in males was not at issue in this Complete Response, this Medical Reviewer examined the efficacy of 1.75 mg in males as a means to test whether Intermezzo would be effective in a population that generally had lower plasma exposure than females. An ANOVA analysis of the ZI-06-10 dataset supplied by the Sponsor using LPS post MOTN awakening by treatment was performed. A test for statistical significance was performed using Dunnett's test with the placebo arm as the control treatment. Both the 3.5 mg and 1.75 mg treatments were effective (**Figure 3**;p=0.03 for 1.75 mg, < 0.0001 for 3.5 mg). This lends further support that the 1.75 mg dose can be effective in females, since for a given dose, the plasma zolpidem concentrations are often higher than in males.

Figure 3 LPS Post MOTN Awakening in Males by Dose Group



Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Placebo	24	37.4375	3.4827	30.490	44.385
SZT 1.75 mg	24	25.2917	3.4827	18.344	32.240
SZT 3.5 mg	24	15.3646	3.4827	8.417	22.312

Comparisons with a control using Dunnett's Method

Control Group = Placebo

|d|	Alpha
2.25821	0.05

Level	Abs(Dif)-LSD	p-Value
Placebo	-11.1	1.0000
SZT 1.75 mg	1.023	0.0302*
SZT 3.5 mg	10.95	<.0001*

Positive values show pairs of means that are significantly different.

Figure Legend

This figure demonstrates the 95% confidence intervals (green diamonds) for the LPS (Y axis, in minutes) in males in the PBO, 1.75 mg, and 3.5 mg dose groups from the ZI-10 Study. The middle bar in each diamond represents the group mean. Individual data points are represented by the dots rising vertically in each dose group. The black horizontal line crossing through the 1.75 mg diamond represents the overall mean of the three groups. Descriptive statistics of dose group, N, mean standard error, and the 95% confidence limits. Statistical testing using the Dunnett's Test with the PBO groups as a control arm is presented in the bottom panel.

5 Review of Safety

Safety Summary

The safety has been evaluated in the previous Medical Reviewer and CDTL reviews. Comments from this MR will focus on materials sent in the Complete Response comparing adverse events in the 1.75 and 3.5 mg dose groups in females.

5.1 Methods

Adverse events for the ZI-10 and -12 studies were presented by the Sponsor. This Medical Officer specifically looked at

- the incidence rate between females at 1.75 mg and males at 3.5 mg; and
- the incidence rate between females at 1.75 and 3.5 mg.

5.2 Supportive Safety Results

5.2.1 Common Adverse Events

Table 6 Adverse Events for Females (1.75 mg) and Males (3.5 mg) from the ZI-10 Study

Table 6: Summary of Treatment- Related Adverse Events (≥1%) in Double-Blind, Cross-Over, Placebo-Controlled Sleep Laboratory Study

	Women		Men	
	1.75 mg (n=58)	Placebo (n= 57)	3.5 mg (n=24)	Placebo (n=24)
MedDRA System Organ Class/ Preferred Term				
Gastrointestinal disorders				
Diarrhea	0	0	0	1 (4.2%)
Nausea	0	1 (1.8%)	0	0
Oral pain	0	0	0	1 (4.2%)
Infections and infestations				
Urinary tract infection	1 (1.7%)	1 (1.8%)	0	0
Investigations				
Blood pressure increased	0	0	1 (4.2%)	0
Glucose urine present	1 (1.7%)	0	0	0
Nervous System Disorders				
Headache	0	0	1 (4.2%)	0
Paraesthesia mucosal	0	1 (1.8%)	0	0
Paraesthesia oral	0	1 (1.8%)	0	0
Sedation	0	1 (1.8%)	0	1 (4.2%)
Skin and subcutaneous tissue disorders				
Dermatitis contact	0	0	1 (4.2%)	0

Analysis datasets for subgroup analyses supplied in Section 5.3.5.3

Table 7 Adverse Events at the 3.5 mg Dose Level from the ZI-12 Study

Table 7: **Summary of Treatment Emergent Adverse Events (≥1%) in 3.5 mg[a] Outpatient, Double-Blind, Parallel-Group, Placebo-Controlled Study**
[a]3.5 mg is double the recommended dose in women of 1.75 mg

MedDRA System Organ Class Preferred Term	Women		Men	
	3.5-mg Intermezzo (n=107)	Placebo (n=94)	3.5-mg Intermezzo (n=43)	Placebo (n=51)
Blood and lymphatic system disorders				
Lymphoadenopathy	0	1 (1.1%)	0	0
Gastrointestinal disorders				
Abdominal pain	0	1 (1.1%)	1 (2.3%)	1 (2.0%)
Abdominal pain upper	0	0	1 (2.3%)	0
Diarrhea	0	0	1 (2.3%)	0
Dyspepsia	0	1 (1.1%)	0	0
Nausea	2 (1.9%)	0	0	1 (2.0%)
Stomatitis	0	0	1 (2.3%)	0
Vomiting	0	0	1 (2.3%)	0
General Disorders and Administration Site Conditions				
Fatigue	1 (0.9%)	0	1 (2.3%)	0
Feeling of relaxation	0	0	1 (2.3%)	0
Immune System Disorders				
Seasonal allergy	0	1 (1.1%)	0	0
Infections and Infestations				
Bronchitis	0	1 (1.1%)	0	0
Fungal infection	1 (0.9%)	1 (1.1%)	0	0
Nasopharyngitis	0	2 (2.1%)	0	3 (5.9%)
Pelvis inflammatory disease	0	1 (1.1%)	0	0
Sinusitis	0	1 (1.1%)	0	0
Upper respiratory tract infection	1 (0.9%)	1 (1.1%)	0	0

Analysis datasets for subgroup analyses supplied in Section 5.3.5.3

Injury, Poisoning, and Procedural Complications				
Animal bite	0	1 (1.1%)	0	0
Arthropod bite	0	0	0	1 (2.0%)
Joint sprain	0	2 (2.1%)	0	0
Muscle strain	1 (0.9%)	1 (1.1%)	0	0
Investigations				
Blood glucose increased	0	1 (1.1%)	0	0
Body temperature increased	0	0	1 (2.3%)	0
Metabolism and Nutrition Disorders				
Hyperglycemia	0	1 (1.1%)	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0	0	0	1 (2.0%)
Back pain	0	1 (1.1%)	0	1 (2.0%)
Muscle spasms	0	1 (1.1%)	0	0
Nervous System Disorders				
Headache	3 (2.8%)	1 (1.1%)	1 (2.3%)	1 (2.0%)
Sinus headache	0	1 (1.1%)	0	0
Somnolence	1 (0.9%)	0	0	2 (3.9%)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	1 (0.9%)	1 (1.1%)	0	0
Nasal congestion	0	1 (1.1%)	0	0
Postnasal drip	0	1 (1.1%)	0	0
Skin and subcutaneous tissue disorders				
Pruritus generalised	0	0	1 (2.3%)	0

Medical Reviewer's Analysis and Comments: The incidence and type of adverse events in the ZI-10 Study appear similar between the 1.75 mg dose group in females and 3.5 mg in males (**Table 6**). These data are, however, derived from relatively small studies, so the data may not be generalizable. The ZI-10 study is a crossover design, so the adverse event data may not be comparable to cohorts in the 3.5 mg group of the ZI-12 study because of prior drug exposure, particularly for subjects dosed first with 1.75 mg in ZI-10 and because of the longer duration of dosing in the ZI-12 study.

5.3 Other Safety Explorations

5.3.1 Time Dependency for Adverse Events

Medical Reviewer's Analysis and Comments: The Sponsor proposed a second means of mitigating the concern over residual zolpidem plasma levels[1] by proposing to (b) (4) While in principle, every labeling restriction

1 In addition to lowering the dose for females to 1.75 mg

could enhance safety; this reviewer finds the proposal essentially redundant with the 4 hour anticipated sleep time labeling and without significant potential effect. The proposed labeling already contains a recommendation to only dose Intermezzo when there are at least 4 hours of sleep time remaining. (b) (4) [redacted]. On the other hand, there may be an advantage in keeping the language of the labeling simpler in terms of not having potentially conflicting advise to the prescriber.

6 Appendices

6.1 Additional PK Investigations by Medical Reviewer

6.1.1 Analysis of Postdose Zolpidem Concentrations by Gender and Dose

Figure 4 Distribution of Plasma Zolpidem Concentrations 3 hours Post-dose by Gender and Dose

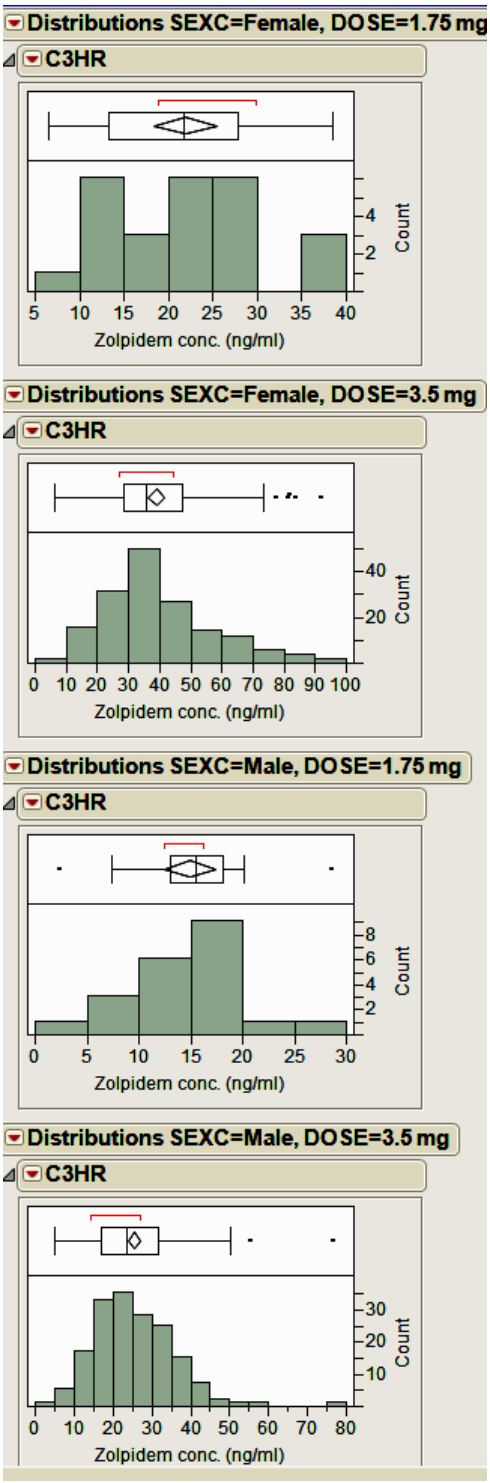


Figure Legend

Distribution plots for individuals (N on Y-axis) versus zolpidem plasma level (X-axis) at the 3 hr post dose interval. A box and whisker plot overlays each histogram.

In the top plot, containing data for females in the 1.75 mg dose group, the range is (6.4-38.5 ng/ml), the mean is 21.9 ng/ml (90%CI: 18.4,25.5).

In the second plot, containing data for females in the 3.5 mg dose group, the range is (6.2-91.8 ng/ml, the mean is 39.0 ng/ml, (90%CI: 36.4,41.5).

In the third plot, containing data for males in the 1.75 mg dose group, the range is (2.4-28.5 ng/ml, the mean is 14.9 ng/ml, (90%CI: 12.4, 17.3).

In the last plot, containing data for males in the 3.5 mg dose group, the range is (4.9-76.4 ng/ml), the mean is 25.4 ng/ml, (90%CI: 23.8, 26.9).

Figure 5 Distribution of Plasma Zolpidem Concentrations 4 hours Post-dose by Gender and Dose

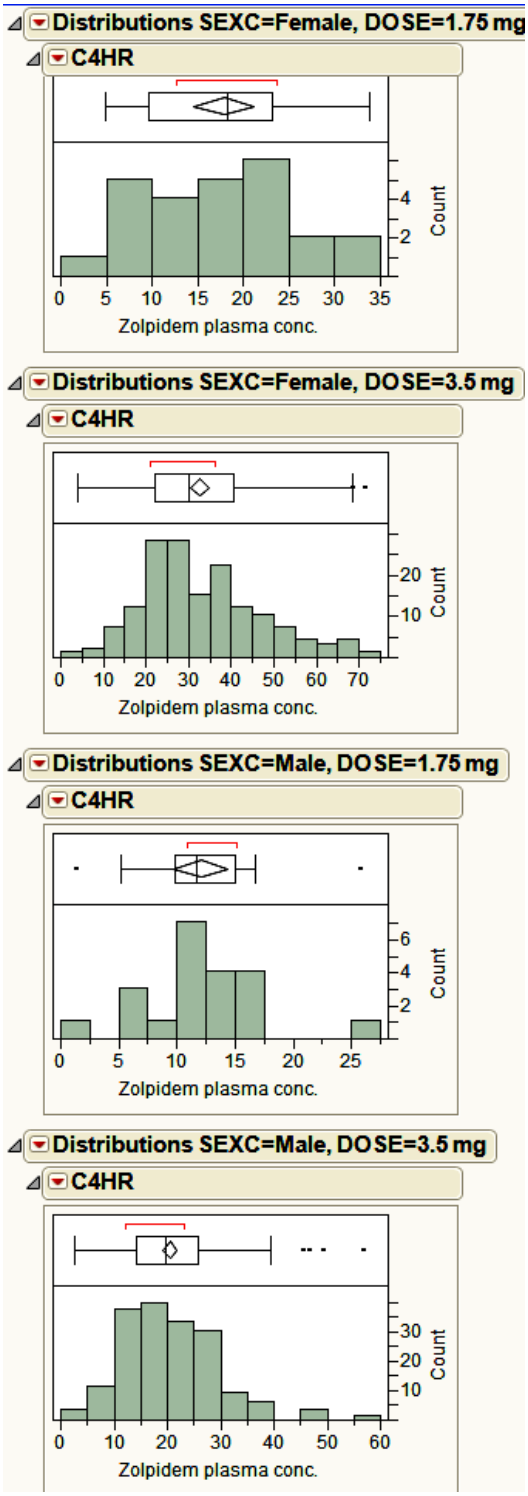


Figure Legend

Distribution plots for individuals (N on Y-axis) versus zolpidem plasma level (X-axis) at the 4 hr post dose interval. A box and whisker plot overlays each histogram.

In the top plot, containing data for females in the 1.75 mg dose group, the range is (4.9-33.8 ng/ml), the mean is 17.8 ng/ml (90%CI: 14.5, 21.2).

In the second plot, containing data for females in the 3.5 mg dose group, the range is (3.9-71.5) ng/ml, the mean is 32.6 ng/ml, (90%CI: 30.4, 34.8).

In the third plot, containing data for males in the 1.75 mg dose group, the range is (1.3-25.8 ng/ml, the mean is 12.1 ng/ml, (90%CI: 9.7, 14.4).

In the last plot, containing data for males in the 3.5 mg dose group, the range is (2.5-56.9 ng/ml), the mean is 20.5 ng/ml, (90%CI: 19.2, 21.8).

Figure 6 Distribution of Plasma Zolpidem Concentrations 5 hours Post-dose by Gender and Dose

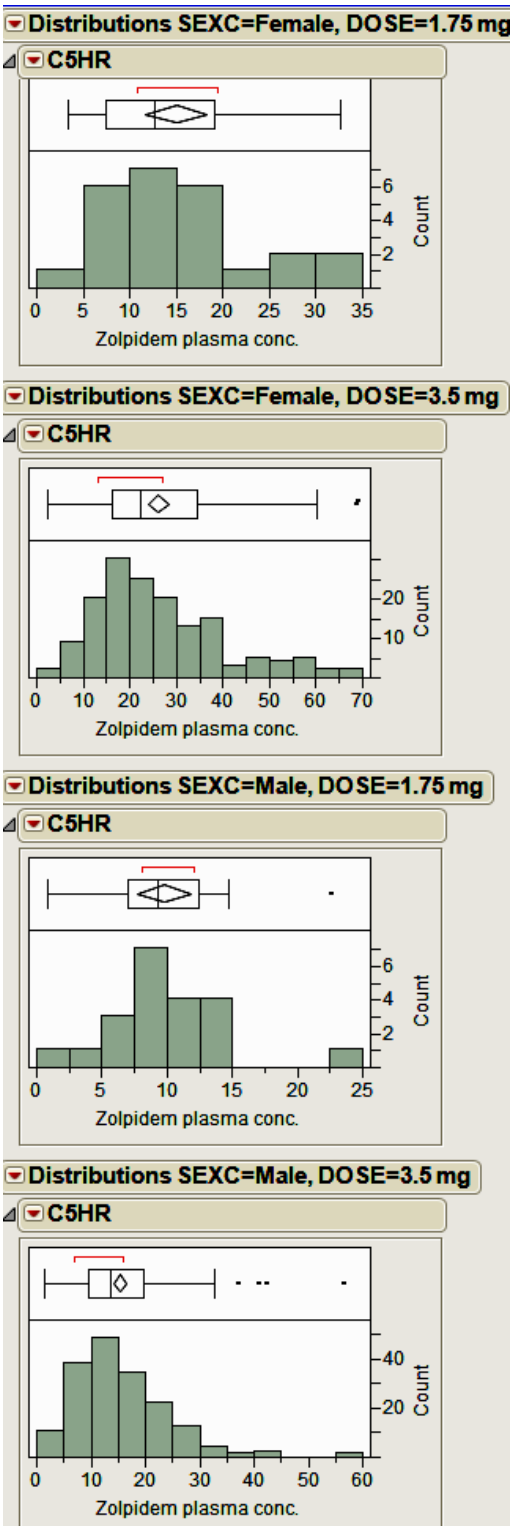


Figure Legend

Distribution plots for individuals (N on Y-axis) versus zolpidem plasma level (X-axis) at the 5 hr post dose interval. A box and whisker plot overlays each histogram.

In the top plot, containing data for females in the 1.75 mg dose group, the range is (3.5-32.6 ng/ml), the mean is 15.0 ng/ml (90%CI: 11.7, 18.3).

In the second plot, containing data for females in the 3.5 mg dose group, the range is (205-69.0) ng/ml, the mean is 26.2 ng/ml, (90%CI: 24.0, 28.4).

In the third plot, containing data for males in the 1.75 mg dose group, the range is (0.8-22.5 ng/ml, the mean is 9.8 ng/ml, (90%CI: 7.8, 11.9).

In the last plot, containing data for males in the 3.5 mg dose group, the range is (1.4-56.4 ng/ml), the mean is 15.4 ng/ml, (90%CI: 14.1, 16.6).

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/s/

CHRISTOPHER D BREDER
11/02/2011

RONALD H FARKAS
11/15/2011

Cross-Discipline Team Leader Review

Date	7/1/2011
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22328, supplement #33
Applicant	Transcept Pharmaceuticals
Date of Submission	January 14, 2011
PDUFA Goal Date	July 14, 2011
Proprietary Name / Established (USAN) names	Intermezzo/zolpidem tartrate
Dosage forms / Strength	1.75 mg / 3.50 mg
Proposed Indication(s)	Insomnia following middle-of-the-night awakening
Recommended:	Complete Response

1. Introduction

The original NDA application for Intermezzo received a Complete Response (CR) Letter on October 28, 2009. The Division agreed that efficacy for insomnia following middle-of-the-night (MOTN) awakening was 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. Both of these risks appeared potentially to be increased compared to other zolpidem products by the MOTN-dosing of Intermezzo.

The Division indicated in the CR letter that it appeared necessary for the sponsor to demonstrate the following:

1. That Intermezzo, when taken as directed, does not unacceptably impair driving ability.
2. That dosing errors can be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety can be shown to be acceptable.

The Division also stated in the CR letter that alternative packaging might help minimize the risk of dosing errors.

At the End-of-Review Meeting with the sponsor on January 20, 2010, the sponsor proposed alternative individual-dose packaging of Intermezzo that, on face, appeared to the Division to decrease concerns about risk of inadvertent re-dosing of Intermezzo in a single night. However, the Division remained concerned that the alternative packaging might not adequately address the risk of impaired next-day driving from inadvertent dosing with less than 4 hours of bedtime remaining. The Division

proposed that the sponsor might study the risk of dosing errors in a patient-use study prior to approval. The sponsor, however, proposed conducting a study only of patient understanding of dosing instructions, arguing that a study that attempted to observe directly if patients actually followed dosing instructions would be neither possible nor useful, because patient behavior in the study would not be generalizable to actual clinical use. The Division agreed to consider the sponsor's argument in their Complete Response.

At the post-action meeting there was also agreement that the sponsor would submit to the division for review and agreement a proposal for a driving study to evaluate next-day impairment from Intermezzo. On March 24, 2010, a teleconference was held to discuss the sponsor's proposed driving study. The Division agreed that the driving study (ZI-18) was of acceptable design to address the question.

Importantly, during the current review cycle, the division became concerned that potentially impairing levels of residual zolpidem were occurring in patients at the high end of the distribution of blood levels. The division therefore asked the sponsor to conduct additional pharmacokinetic and pharmacodynamic analysis to determine if specific baseline patient characteristics, such as gender and body weight, could predict high blood levels. The sponsor submitted this additional analysis on May 26, 2011 (Amendment 40).

Dr. Carole Davis was the primary clinical reviewer for this resubmission. Dr. Loretta Holmes was the primary reviewer from the Division of Medication Error Prevention and Analysis (DMEPA). Robin Duer was the primary reviewer from the Division of Risk Management (DRISK). Dr. Stephen Sun was the primary reviewer from the Controlled Substance Staff (CSS). Dr. Tristan Massie was the primary reviewer from the Office of Biostatistics (OB), and Dr. Jagan Parepally was the primary reviewer from the Office of Clinical Pharmacology (OCP).

2. Sponsor Response

a. Comparative Safety Profile of Intermezzo

As a general argument for the safety of Intermezzo, the sponsor first argues that the overall safety profile of Intermezzo is superior to other drugs currently used for insomnia, as follows:

- MOTN insomnia usually does not occur every night, but current drugs for sleep maintenance must be taken prophylactically, essentially every night. Since Intermezzo would be taken only when needed, it would decrease overall exposure, thus decreasing overall risk of adverse drug events.
- A significant percentage of patients misuse drugs approved only for bedtime dosing, instead taking them as MOTN treatment. This misuse is supported by the sponsor's epidemiological study, *Middle of the night (MOTN) hypnotic use among insured Americans with hypnotic prescriptions*,' by Kessler et al. The

sponsor argues that such off-label use places patients at higher risk of next-day residual impairment compared to use of Intermezzo.

Dr. Davis generally agrees with the sponsor about the potential advantages of a low-dose, PRN form of zolpidem for MOTN use, but remains concerned that an adequately safe MOTN dose/usage has not been identified.

CDTL discussion: I agree with Dr. Davis.

b. Previous Clinical Studies

Also as part of their general argument for the safety of Intermezzo, the sponsor argues that the clinical studies previously submitted demonstrate lack of unacceptable next-day impairment from Intermezzo. The sponsor particularly notes that subjective self-assessments of function, sleepiness, etc., were improved by Intermezzo.

CDTL discussion: Subjective measures of next-day function do not provide adequate reassurance about safety because individuals can be unaware of their own level of impairment. The sponsor notes that in ZI-06-010 there was no change in Digit Symbol Substitution Test (DSST) in the morning following Intermezzo dosing. However, the sensitivity of this test for impairment, and driving impairment in particular, is questionable. For example, the DSST is administered over ≈2 minutes, and may have limited relevance as a measure of the sustained attention and wakefulness needed for safe driving. With no evidence of assay sensitivity, negative results aren't interpretable.

c. Redosing Errors

The sponsor originally propose (b) (4) As first presented at the January 20 End-of-Review Meeting, and presented in the current resubmission, the sponsor proposes that the following aspects of the packaging and labeling system adequately minimizes the potential of this type of dosing error:

- 'Unit-Dose Pouch', designed to limit bedside access to a single dose, and to allow the empty package to serve as a reminder that a dose was taken
- Patient instructions for use

The sponsor argues that risk of re-dosing error is minimized by having the patient plan and prepare before bed for MOTN dosing, thus decreasing decision making and the risk of error when, for example, the patient might be cognitively impaired by a previous dose of Intermezzo.

The sponsor concludes from their labeling comprehension study that patients can both understand and apply dosing instructions to arrive at the correct dose in various use situations.

Dr. Holmes conducted a detailed review of the labeling comprehension study. She concluded that the design of the study was adequate to assess patient understanding of the 4-element packaging system, and that the results appeared to support the premise that patients are able to understand and use the packaging system/instructions correctly. Dr. Holmes noted that only one subject met 'low literacy' criteria, such that it was unclear if lower literacy patients (8th grade or lower literacy) would understand and use the packaging system correctly.

Dr. Davis concludes that the packaging system and instructions are adequate to address the risk of inadvertent redosing in a single night.

CDTL discussion: Dr. Holmes notes that patients with low literacy were under-represented in the comprehension study, but does not express concern that the patient material is written at an inappropriately high reading level. I do not think that additional patient comprehension studies would be necessary before approval. However, post-marketing pharmacovigilance should be particularly alert for dosing errors that might be attributed to low literacy.

The Division expressed at the End-of-Review meeting that the proposed packaging and labeling on-face appeared to decrease concerns about risk of inadvertent redosing. The original proposed packaging and instructions (b) (4) **In contrast, with the new packaging and instructions, there is a clear separation of activities that would occur with taking a first dose versus a second dose. For the first dose, *before beginning sleep*, the patient would take a single dose packet from the Intermezzo box stored away from the bed, and place the single dose next to the bed. On waking MOTN, the patient would take that dose. Once that dose was taken, any further action of the patient to get another dose would be a large departure from the usual dosing method, requiring the patient to leave bed, get another dose from the box, etc. Additional reminders, like the empty packet at bedside, would also help reinforce that a dose had already been taken that night. I therefore conclude that the risk of redosing has been adequately mitigated.**

d. Dosing with less than 4 hours time in bed

The sponsor argues that the risk of dosing with less than 4 hours time remaining in bed is also adequately addressed by the new packaging and labeling. The dosing time chart would obviate the need for calculation of time left to sleep, minimizing

errors. In addition, the dosing wheel would a) reinforce to patients, before going to sleep, the latest time a dose could be taken in the night, and b) present a pre-set reference for that time when the patient awoke at night, such that essentially no additional reading of dosing tables or instructions would be needed.

The sponsor argues that a study that attempted to directly observe patient ability to follow dosing instructions, as discussed by the Division at the End-of-Review meeting, would be neither possible nor useful, as follows:

- **Intermezzo is safe even if misdosed**: Even if patients misdose, and take Intermezzo with only 3 hours of sleep remaining, zolpidem blood levels 3 hours after dosing would not be greater than zolpidem blood levels 7 hours after dosing (per labeling instructions) other zolpidem sleep products, including Ambien CR, Zolpimist, and Edluar. Since FDA considers blood levels from these other drugs to be safe, it follows that Intermezzo should be considered safe even if taken with only 3 hours of sleep time remaining. A study to determine if such dosing errors occurred is thus unnecessary because no safety risk could result from such errors.

  CDTL comment: As discussed in detail in Section 4, blood levels from Intermezzo in patients *at the high end of the distribution of exposures* are of concern, even at 4 hours post-dosing and later. Arguments based on mean blood level fail to address this key aspect of the problem.

  Also, as discussed in Section 5, because of high inter-study variability, post-hoc, cross-study comparisons of zolpidem blood levels from various products are not reliable.

- **Misdosing Intermezzo is safer than misdosing other sleep drugs**: The sponsor argues that the report of Kessler et al. shows that patients purposefully treat MOTN awakenings with hypnotics intended for bedtime use. Since the dose of zolpidem in Intermezzo is low, it would be safer to misdose Intermezzo than to take a drug intended for bedtime use for a MOTN awakening. A study of dosing errors is therefore unnecessary because even if dosing errors occurred with Intermezzo, overall patient safety in the community would be improved.

  CDTL comment: There is no evidence about the type or frequency of dosing errors that would occur in the community with Intermezzo, or that overall patient and community safety would be improved.

- **Validity of results**: Patient behavior changes under observation, such that any results from a study would not be applicable to actual use.

  CDTL comment: **Observed patients would seemingly be more likely to dose *correctly*. While a 'negative' study would not exclude dosing errors under clinical conditions, a positive finding of errors would still seemingly be valid.**

- **Feasibility:** If conducted with patients at home, the study would be intrusive due to use of a camera or other monitor in the bedroom, such that patients would not enroll.

  CDTL comment: The at-home efficacy study for Intermezzo (ZI-12) appeared to show misdosing through patient reports using an automated voice-response system. Overly-intrusive monitoring appears not to be necessary to document patient behavior.

- **Interpretability**: There is no external way to distinguish inadvertent from deliberate dosing too late in the night. Patients do deliberately misdose, so any finding of misdosing might be attributable to deliberate, not inadvertent misuse.

  CDTL comment: What constitutes 'misuse' may not be clear; under ordinary clinical use, patients will deviate to some degree from labeled directions, and the safety consequences of this deviation need to be taken into consideration in evaluating overall drug safety.

- **Packaging and labeling mitigates risk**: the potential for misdosing is adequately mitigated by packaging and labeling.

  CDTL comment: This review finds that packaging and labeling *does* communicate instructions clearly; however, risk from blood levels that would occur with 'as labeled' use has not been adequately addressed.

- **Patient self-assessment**: The sponsor argues that FDA has historically relied on next-morning patient self-assessment of drowsiness to minimize potential harm. Even if patients misdose, morning self-assessment will detect impairment and prevent harm.

  CDTL comment: While patient self-assessment might have some value, the sponsor presents no evidence of the degree to which risk might be decreased by such labeling. The fact that some patients might be able to self-identify as impaired does not logically mean that most or all patients would be able to do so. In the sponsors PK/PD studies, there was no clear correlation between 'VAS for alertness' and zolpidem blood levels.

Dr. Davis concludes that the instructions, cautions, and dosing aids likely decrease the risk of misdosing as much as can be achieved.

CDTL Discussion:
As discussed above, the sponsor's arguments that late dosing can't be studied aren't compelling. However, as discussed in the CDTL memo for the original NDA submission, data from the Intermezzo outpatient efficacy study suggests that it is *already established* that dosing with less than 4 hours of sleep remaining is likely to occur fairly frequently with use of Intermezzo.

- **Seven subjects in the 4-week subjective study, 5 on zolpidem (3.3%), and 2 on placebo (1.4%), dosed after reporting that they had less than 4 hours of sleep remaining. The study was designed so that patients were required to call an interactive voice response (IVRS) system before dosing, and patients were given permission over the telephone to dose only if 4 hours were left of sleep time. These patients called the IVRS system, were denied permission to dose, but dosed anyway. It was not possible to differentiate purposeful disregard for the dosing instructions versus confusion on the part of the patients.**
- **Patients were instructed to call the IVRS system both before dosing, and about 30 minutes after awakening in the morning. About 2% of patients in each week of the study made the two calls separated by less than 4 hours, indicating the patients were presumably active less than 4 hours after dosing. There were no patients with calls separated by less than 3 hours.**

While the current packaging and instructions were not used in the efficacy study, it seems unlikely that these measures would decrease dosing errors more effectively than the much more structured procedures used in the clinical trial (including explicit requirement for permission to dose). Another study of patient ability to follow directions therefore appears likely to be of limited benefit since previous data already indicates that dosing with less than 4 hours of sleep remaining is *likely to occur*. Attempts to determine if misdosing is intentional or unintentional appear unlikely to be largely interpretable, since as the sponsor notes, patients may not accurately report their motives.

Both from the specific findings from the Intermezzo outpatient efficacy study, and from general clinical experience in other settings, dosing within about 30- to 60 minutes of labeled instructions appears be the limit of compliance that can be expected. Therefore, I recommend that Intermezzo should only be approved if it can be shown to have acceptable risks as actually used.

As an additional note, as discussed in the review of the original submission, patients awakening from sleep can experience 'sleep inertia' which includes a variable period of cognitive and psychomotor impairment. This raises concern that patients might be more likely to misdose a MOTN insomnia treatment than to misdose an insomnia treatment taken before initiating sleep. However, I agree with the sponsor's argument in the original submission that the level of arousal (and perhaps hyperarousal) of insomnia patients when experiencing difficulty falling asleep MOTN is likely adequate to allow perception of the time of night, such that directions for use, incorporating the various aids the sponsor has proposed, can be followed to within about 30- to 60 minutes.

3. Driving Study

Design

The driving study was designed to evaluate if Intermezzo 3.5 mg impaired driving, either at 4 hours after dosing ('Intermezzo 4 hours'), or at 3 hours after dosing ('Intermezzo 3 hours'). Evaluation of driving began immediately at the 4- or 3-hour time point after dosing, such that patients were actually awakened, respectively, at about 3.25 or 2.25 hours after dosing. Zopiclone 7.5 mg dosed 9 hours previously was included as a positive control of impairment (zopiclone is not marketed in the U.S., but is widely used in Europe at this dose for insomnia). A 4-way crossover design was used, with 20 adult male and 20 adult female healthy subjects (without insomnia), with each subject tested for each condition (with the exception of placebo, which did not attempt to differentiate between placebo given 3- versus 4 hours from the start of the driving study).

The study was conducted by Dr. Vermeeren and associates at Maastricht University, with the primary endpoint based on 'on road' measurement of 'standard deviation of lateral position' (SDLP) during a 1 hour drive on the public highway. SDLP measures how well a subject is able to maintain the vehicle in a steady position relative to the left boundary of the driving lane. Since baseline SDLP differs for different individuals, drug effect is evaluated through change in an individual's SDLP after drug.

A 'symmetry analysis' was used for the primary outcome, in which the proportion of subjects whose SDLP worsened was compared to the proportion of subjects whose SDLP improved to that same degree. If the proportion with impairment was greater than the proportion that improved, impairment would be suggested. The primary threshold change in SDLP chosen was 2.5 cm because, while it does not necessarily separate impaired from unimpaired drivers, it is the average impairment that has been reported in SDLP for drivers with a blood concentration of ethanol of 0.05%, a level that is the legal limit for driving in many countries (the legal limit is 0.08% in the United States). In addition, because the 2.5 cm change is not a 'bright line' of impairment, a range of thresholds between 1.75 cm and 6.5 cm were also examined.

The standard deviation of speed (SDS) was also examined as a secondary endpoint.

Driving Results

Early terminations:

The driving test was terminated for somnolence (verbatim: 'subject fell asleep during driving') for 2 subjects after zopiclone, and for one subject after 'Intermezzo 3-hours,' at 44 minutes after the start of the driving test (thus, at 3 hours, 44 minutes after dosing). The subject that fell asleep after 'Intermezzo 3 hours' was a 23-year-old women, weighing 53 kg (the lightest subject of the 40 studied).

SDLP Symmetry analysis:

For the symmetry analysis, the terminated tests were taken to be impaired for every SDLP threshold tested.

For zopiclone, the sponsor concludes that the symmetry analysis showed a statistically significant impairing effect across all SDLP thresholds up to 5.5 cm, confirming assay sensitivity.

For Intermezzo 3 hours the sponsor concludes that the symmetry analysis showed a statistically significant impairing effect, up to and including the 4.0 cm threshold. The mean difference in SDLP between Intermezzo and placebo was 1.5 cm, which was also statistically significant, although the sponsor suggests that it was not clinically meaningful because it was below the 2.5 cm threshold. The sponsor concludes that if Intermezzo is taken 3 hours before driving, it would produce some effects on next-morning driving performance. However, the sponsor notes that the 3 hour test actually required waking patients 2.25 hours after dosing, such that the test really reflects less than '3 hours in bed' after dosing.

For Intermezzo 4 hours, the sponsor concludes that the symmetry analysis for Intermezzo 4 hours did not show a statistically significant effect on any of the pre-specified thresholds, and that Intermezzo therefore does not cause clinically meaningful impaired driving. The sponsor concludes that while a nominally statistically significant difference was shown on analysis of mean SDLP of 0.8 cm, the magnitude of this difference was small, and not clinically meaningful.

Table 1: Intermezzo 4 Hours Symmetry Analysis

Levels of Threshold in Relation to Impaired Driving Performance and P-values

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZST 4h	1.75	8	29	3	0.200	0.075	2.27	0.2266
	2	6	33	1	0.150	0.025	3.57	0.1250
	2.25	5	34	1	0.125	0.025	2.67	0.2188
	2.5	5	34	1	0.125	0.025	2.67	0.2188
	2.75	4	36	0	0.100	<.001	4.00	0.1250
	3	3	37	0	0.075	<.001	3.00	0.2500
	3.25	2	38	0	0.050	<.001	2.00	0.5000
	3.5	2	38	0	0.050	<.001	2.00	0.5000
	3.75	2	38	0	0.050	<.001	2.00	0.5000
	4	1	39	0	0.025	<.001	1.00	1.0000

Standard Deviation of Speed (SDS)

SDS was included as a secondary endpoint, but the sponsor notes that it is not a 'primary' measure of impairment in published literature, and may have less sensitivity for impairment than SDLP. Mean change in SDS versus placebo was 0.16 km/hr for zopiclone (p=0.01), 0.15 km/h for Intermezzo 4 hours (p=0.01), and 0.08 km/hr for Intermezzo 3 hours (p=0.22). The sponsor notes that the greater impairment in SDS for Intermezzo 4 hours versus 3 hours lacks biological plausibility.

Sponsors Overall Conclusions From Driving Study
The sponsor states that the driving study fully supports previous safety conclusions: no previous studies found evidence of residual impairment, and both phase 3 studies showed evidence of improved ability to function (ZI-06-010) and improved morning alertness (ZI-12). The sponsor further states that the results indicate that Intermezzo 3.5 mg has a 'minimal risk' of producing effects on driving performance in the morning 4 hours post-dose, and a statistically significant, but small effect, on driving performance, when driving occurs 3 hours post-dose. However, the sponsor stresses that because the driving tests were conducted precisely 3 or 4 hours after Intermezzo dosing, the time post-dose in terms of traditional drive-time designations post-waking should be considered 2 or 3 hours after dosing, respectively.

Dr. Massie concludes that study ZI-18 provides some evidence of impairment of next day driving caused by Intermezzo 4 hours. The sponsor's primary asymmetry analysis did not find statistically significant treatment effects at any SDLP threshold. However, the following analyses were nominally positive:

- Symmetry analysis at up to 1.5 cm. (p=0.04, 12 impaired vs. 3 improved)
- Analysis as continuous variable, difference versus placebo of 0.83 cm (p=0.02)

At 3 hours, Dr. Massie notes that the symmetry analysis showed nominal significance at numerous cutpoints, and concludes that Intermezzo 3 hours leads to impaired driving as assessed by SDLP.

Analysis of impairment by gender may have shown a trend for increased impairment in women versus men at both 3 and 4 hours, particularly at lower levels of impairment. For example, for Intermezzo 4 hours, at the 1.5 cm cutoff, 3 men were improved and 4 were impaired, while for women none improved and 8 were impaired.

There were no subjects age 65 years or older. There was a trend for greater impairment at age <31.5 versus >31.5.

Dr. Massie discusses potential shortcomings of assessing driving impairment using SDLP as done in this study, including, for example, that averaging SDLP over the entire drive would obscure isolated but more important events of loss of car control, like going out of the lane.

As noted above, Dr. Massie finds that the assumption made that placebo administered at the 2 different times had the same effect appears justifiable based on

lack of differences in SDLPs between groups of patients assigned to the different placebo times.

Dr. Davis finds the highway study to be well-designed and conducted, but notes that interpretation of findings was limited by lack of zolpidem blood levels from patients. She notes that at the 2.5 cm SDLP threshold of driving impairment, 5 of 40 subjects (12.5%) taking Intermezzo would be considered impaired, and that questions regarding which patients might be at increased risk of this type of impairment have not been adequately addressed. In particular, Dr. Davis does not consider 'nonsignificant' p-values at 4 hours on the symmetry analysis to provide adequate reassurance of safety.

CDTL:
***Timing of driving test*: The sponsor argues that the tests conducted at 3 and 4 hours post-dosing of Intermezzo should be interpreted as impairment that would actually occur from driving 2 and 3 hours post-dosing, respectively. While I agree that the 3- and 4-hour driving tests should be interpreted in the context of the 'artificial' early wake time used in the study, I do not think that the adjustment claimed by the sponsor is appropriate. While some period of time would ordinarily pass between wake time and driving time, the 45 minutes asserted by the sponsor is longer than would occur for some patients in clinical use. The driving test itself was conducted over 1 hour, as blood levels of drug were decreasing. Impairment would seemingly be greater earlier in the test when blood levels were highest, and lowest an hour later when blood levels were lowest. Thus, it seems reasonable to consider the impairment measured to represent that which occurred roughly half-way through the hour-long test. The tests might then reasonable be considered to represent impairment with close to 3 or 4 hours in bed, respectively.**

***Driving Impairment:* The Intermezzo 3 hour arm was positive in the symmetry analysis for thresholds up to and including 4 cm, indicating impairment likely more severe than occurs from ethanol blood levels of 0.05% (at least as far as can be understood from examination of SDLP). This raises concern that patients that are active only moderately (about 1 hour) before the recommended time would be at an unacceptably high risk of driving impairment. One patient fell asleep during the driving test at 3 hours 44 minutes after dosing. This event is particularly worrisome, because falling asleep while driving is closely associated with crash risk, and the event occurred only 15 minutes before the 4-hour time point from dosing, increasing concern that falling asleep while driving remains a risk of Intermezzo up to nearly 4 hours after dosing.**

The Intermezzo 4 hour arm was not statistically positive in the symmetry analysis at any pre-specified threshold (Table 1). However, I agree with Dr. Massie that there is nominally significant evidence of impairment at SDLP values smaller than 2.5 cm, and that the trend of impairment at higher SDLP values is worrisome.

While SDS as a measure of driving impairment is less well-established than SDLP, the increase in SDS both 3 (nominal p-value 0.22) and 4 hours (nominal p-value 0.01) after Intermezzo is generally supportive of residual impairment.

My overall conclusion from the driving study is that it has *increased* concern that Intermezzo causes unacceptable impairment of driving. As discussed in Section 4, during review of the driving study, the division examined the *distribution* of morning zolpidem blood levels, and found levels to be very high in some patients, particularly women. Study ZI-18 was not designed to quantify impairment in the subgroup of patients at the high end of zolpidem exposure, and the fact that even at 4 hours after dosing there was a trend to impairment increases concern about driving safety for patients with zolpidem levels at the higher end of the observed distribution.

While only a trend, the analysis by gender suggests that impairment might have been greater in women, which would be consistent with the higher blood levels observed in women (see Section 4)

> **Note: On February 28, 2011 the sponsor was asked to submit data addressing how artifacts were removed from the driving study data, with the particular concern that removing data from what is essentially a non-inferiority study could bias findings towards the negative. My review of the methodology found it to be acceptable, and unlikely to risk introducing bias. Dr. Massie examined evidence of impairment in the edited, as well as the unedited data, decreasing his concern about potential introduction of bias towards a null finding.**

4. Risk from Variability of Residual Zolpidem Blood Levels

CDTL note: In the CR letter to the original NDA, the Division noted that the blood levels of zolpidem 4 hours after Intermezzo dosing would still average about 25 ng/ml, and cited published studies about driving impairment after zolpidem dosing, expressed concern that this level might still adversely affect driving ability. Importantly, the present review of the sponsor's complete response concludes that while *average* zolpidem blood levels in a population are a concern, risk is likely particularly high in the subset of patients who have the highest morning blood levels. If even a relatively small percentage of patients taking the drug were impaired in the morning, the drug could not be considered adequately safe.

The sponsor was asked by the Division to reanalyze PK data with a focus on subjects with high blood levels of zolpidem, and to ascertain if patients likely to have high blood levels could be identified by such demographic factors as gender and body weight. The sponsor was further asked to determine the relationship between zolpidem blood

levels and PD response, based on demographic factors. The sponsor reached the following conclusions from this reanalysis:

- Between-subject variability in zolpidem levels was not excessive, generally falling in the range of less than 50%. 'Outliers' with excessive blood levels were not identified; instead, patients at the higher end of the distribution of blood levels reflect expected between-subject variability.
- Cmax and blood level at 4 hours (C4) were higher in women than in men, reaching statistical significance in many cases.
    - The ratios of mean AUC for women divided by AUC for men were: 1.49, 1.44, and 1.48 for Studies -009, -13, and -15 respectively. In two studies (-14 and -17), women did not differ in total AUC; mean ratios for those two studies were 1.03 and 1.16, respectively. Study ZI-16 evaluated plasma concentrations at 3 hours (C3) and 4 hours (C4) after dosage. The ratio of mean values (Female/Male) was 1.76 for C3 and 1.68 for C4.
- Gender differences are partly explained by body weight, inasmuch as gender differences in weight-normalized variables were smaller and generally not significant.
  CDTL note: From inspection of scatterplots of PK parameters by weight and gender, a clear pattern of within-gender effects of weight was not discernable.
- There was no coincidence between PK and PD, and subjects with high exposure were not at risk for excessive or prolonged PD effect. Women are not at risk of residual sedative effects extending beyond 4 hours after dosage, and no other demographic factors had a significant effect on PD (age, body weight, BMI, ethnicity).
    - In study -009, PD response based on DSST was greater in women than men. Scores for women were significantly affected through and including 3 hours after dosage (next measurement taken at hour 4). DSST was more affected in women than men at any given blood level, suggesting that women might have a greater intrinsic sensitivity to zolpidem (Figure 1: PK/PD by Gender, Study -009).
    - In study -16 and -17 there was no difference in PD response in women compared to men.
    - In the two efficacy studies, there was no difference in efficacy (sleep latency) between men and women, or resulting from any other demographic factor.
    - In study -18, the driving study, there was no effect of gender or other demographic factors on driving impairment.

The sponsor makes a number of additional assertions to support that dose adjustment for demographic factors is not warranted:

- Only a small fraction of PD variability is explained by variability in exposure or gender differences.
- There is no established threshold zolpidem concentration associated with efficacy or next-day safety.

CDTL note: In the original submission the sponsor indicated that they selected the dose of Intermezzo largely based on the conclusion from literature studies that a blood level of 25 ng/ml would be effective for sleep latency.

- Other Zolpidem products for insomnia are approved without requirements for dose adjustment based on gender or body weight

Dr. Parepally prepared a table of zolpidem blood levels between 3- and 5 hours after dosing for patients in Intermezzo PK studies (Table 2).

Table 2 : Zolpidem blood levels, hours after dosing

		Above 30 ng/mL			Above 40 ng/mL			Above 50 ng/mL			Above 60 ng/mL		
Study	**N**	**3 hrs**	**4 hrs**	**5 hrs**	**3 hrs**	**4 hrs**	**5 hrs**	**3 hrs**	**4 hrs**	**5 hrs**	**3 hrs**	**4 hrs**	**5 hrs**
-009	M= 13	5	2	1	0	0	0	0	0	0	0	0	0
	F= 11	8	6	3	4	2	1	2	0	0	1	0	0
-13	M=23*	11	4	1	0	0	0	0	0	0	0	0	0
	F=13*	23	17	8	12	10	0	6	2	0	0	1	0
-14	M=9	7	5	4	4	2	1	0	0	0	0	0	0
	F=16	5	2	1	2	1	1	1	1	1	1	0	0
	Fasted												
-15	M=19	8	2	1	3	1	0	1	0	0	0	0	0
	F=15	13	10	2	8	2	2	2	1	0	2	0	0
	Fed												
	M=19	4	3	3	1	1	1	1	0	0	0	0	0
	F=15	6	5	4	1	0	0	0	0	0	0	0	0
-16	M=10	3	1	0	0	0	0	0	0	0	0	0	0
	F=20	17	12	10	10	9	7	9	6	5	6	3	1

* Two data points were included for each subject since the formulations tested (IND formulation and commercial formulation) were bioequivalent.

Dr. Parepally concludes the following regarding PK and PD effects of Intermezzo:

- Zolpidem plasma concentrations (AUC) in females was 30-40% higher compared to males in the pivotal BE study ZI-15.
- There was no 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 presence of a gender difference, and raising concern for possible next day residual effects in these subjects.

- There was no correlation identified between PK and PD for next day residual effects.

Dr. Parepally's overall conclusion was that the PK/PD relationship was not clear from the data submitted, and that it should be studied more, and used to justify the safety of Intermezzo.

Dr. Davis concludes the following regarding the PK and PD effects of Intermezzo:

- Elevated zolpidem levels at 4 hours do not appear to have a direct correlation, in individual subjects, with decreased PD functioning, based on the available data.
- However, the PD tests, including the driving test, can not exclude increased PD effects at higher blood levels.

CDTL Discussion: I disagree with the sponsor's conclusion that residual blood levels of zolpidem in the range observed do not present a risk of next-day impairment. The sponsor identified patients in each PK study that were in the highest 10th percentile for exposure (based on Cmax, AUC, and zolpidem blood level at 4 hours post-dosing). Out of 25 patients they identified, at 4 hours after Intermezzo 3.5 mg, 14 with a blood level above 40 ng/ml, 7 with a level above 60 ng/ml, and one with a blood level of ≈ 80 ng/ml.

- **Zolpidem blood levels in the driving study (ZI-18) were not measured, but levels from the PK studies suggest that the average zolpidem level in the 3-hour arm of the driving study was unlikely to be greater than ≈30- to 40 ng/ml. The 3-hour arm was positive in the symmetry analysis up to and including the 4 cm SDLP threshold (greater impairment than the 2.5 cm cutoff associated with blood alcohol concentration of 0.05%) suggesting clinically meaningful impairment of driving in this range of zolpidem blood levels.**

  It might be argued that the impaired subjects at 3 hours where those who had above-average blood levels, that is, blood levels > 40- or even 50 ng/ml. However, even if the signal for impairment was driven largely by patients with such levels, as noted above, patients commonly have a blood level ≥ 50 ng/ml 4 hours after taking 3.5 mg Intermezzo.

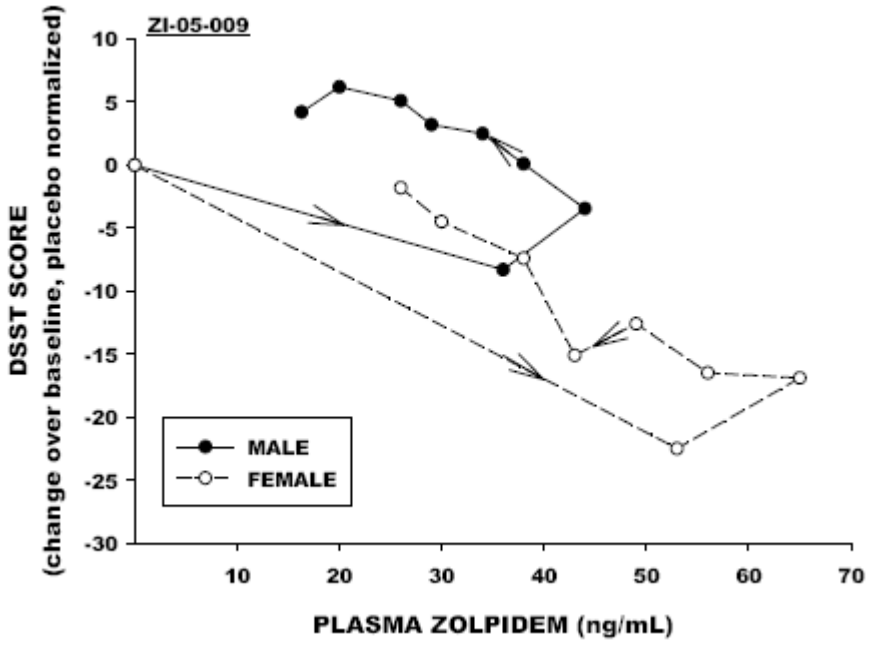
- **Patients at the high end of the distribution of zolpidem levels at 4 hours likely had blood levels about the same as the average Cmax from Intermezzo 3.5 mg in the efficacy studies, a dose shown to be effective for decreasing sleep latency. Moreover, these blood levels are double or more the average Cmax from 1.75 mg Intermezzo, a dose which was also shown to result in a statistically significant decrease in sleep latency (study ZI-06-010). While PD effects of any given zolpidem blood level likely differ to some degree depending on the specific circumstances**

(e.g. whether level is increasing or decreasing), driving with zolpidem levels proven to increase tendency to sleep appears clearly to raise concern that patients will be at increased risk of falling asleep while driving.

- **In study -009, a blood level during the declining phase of between ≈55 and 65 ng/ml was associated in women with a large, about -15 point, statistically significant decrease (impairment) in DSST (Figure 1). In men, performance on the DSST improved to *better* than baseline over time, suggesting a 'practice effect.' If a similar practice effect occurred in women, actual impairment was likely more severe than measured.**

  To put the DSST impairment from Intermezzo into context, Brumback et al[1] found that DSST in light social drinkers on reaching a blood alcohol concentration (BAC) of about 0.08% was about -8 points, while as BAC decreased to 0.05% (a concentration that is the legal limit for driving in many countries), the DSST had returned essentially to baseline (although, again, its difficult to tell if confounding by practice effect was occurring).

Figure 1: PK/PD by Gender, Study -009



[1] Brumback, T, Cao, D, King, A. Effects of Alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers. Drug Alcohol Depend 2007;91:10-17.

In study -16 and -17, in contrast, there was no difference in impairment between men and women on the DSST, even though women similarly had higher zolpidem exposure than men (although in study -17 the gender difference for zolpidem levels was smaller and the absolute blood levels for both men and women were lower). The sponsor appears to dismiss the findings in study -009 as chance because the result was not duplicated on other studies. However, there is concern that the negative studies lacked assay sensitivity; for example, in study -17, no impairment was detected even at 1 hour after dosing.

5. 'Comparative Safety' Argument

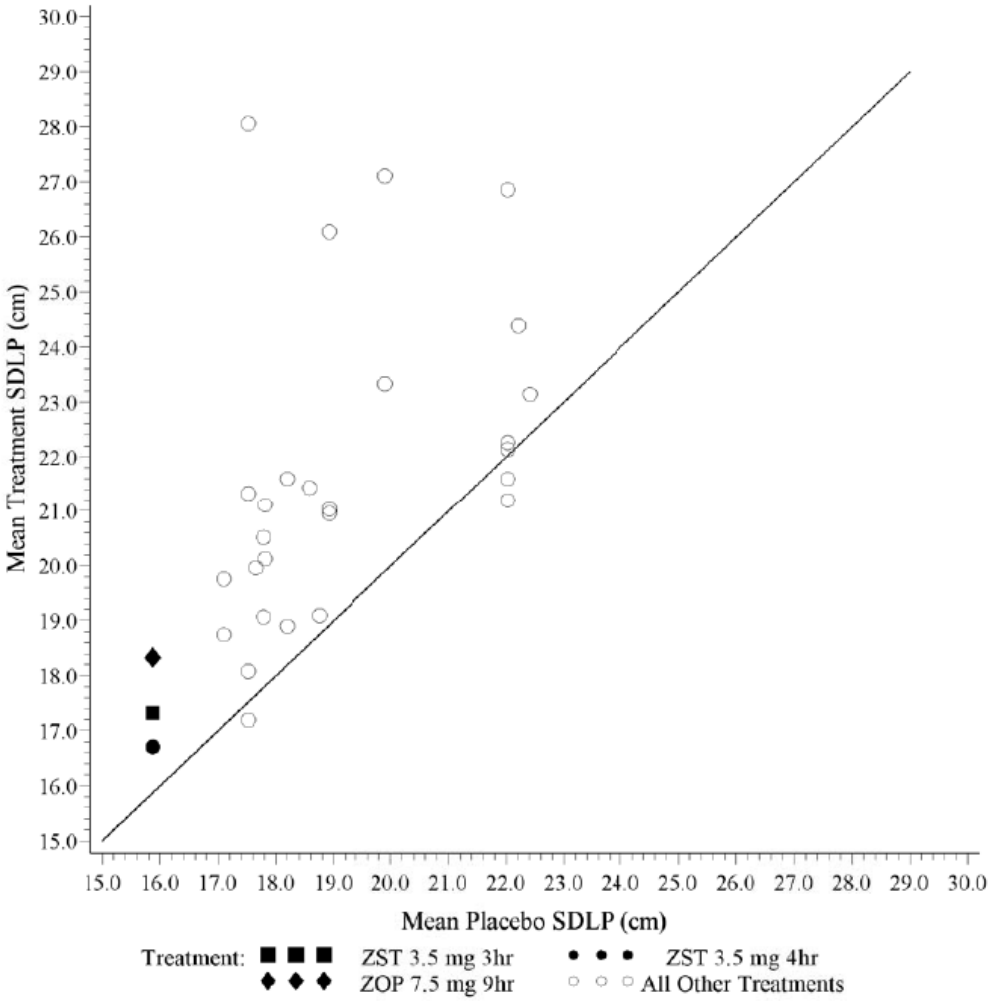
The sponsor additionally argues that residual zolpidem levels from Intermezzo should not be considered unacceptable because a) driving performance after Intermezzo is not as impaired as after some other approved hypnotics [Laska report 70-1029-001], and b) zolpidem levels from Intermezzo are not higher than those reported for other zolpidem formulations [section 2.5.6.2.1]

The sponsor acknowledges that cross-study comparisons are potentially confounded by differences in study conditions, but asserts that despite this limitation, putting results from study -18 'into context' facilitates appraisal of driving risk.

CDTL comment: Cross-study comparison is particularly problematic because mean placebo SDLP for ZI-18 was lower than for any comparator study (Figure 2). Importantly, the thresholds used to evaluate ZI-18 (e.g. 2.5 cm cutoff) were derived in part from these other studies, raising concern that if impairment in SDLP is proportional to the magnitude of baseline SDLP, the cutoffs might be inappropriately large for ZI-18, thus underestimating risk for Intermezzo.

Figure 2: SDLP, ZI-08 versus Published Studies

Figure 1: **Treatment vs. placebo mean SDLP scatter plots of results from studies in Table 1[1] and Table 2[2].** The scatter plot highlights the wide range of SDLP outcomes and reinforces importance of crossover designs for driving studies.



ZST=zolpidem sublingual tablet; ZOP=zopiclone

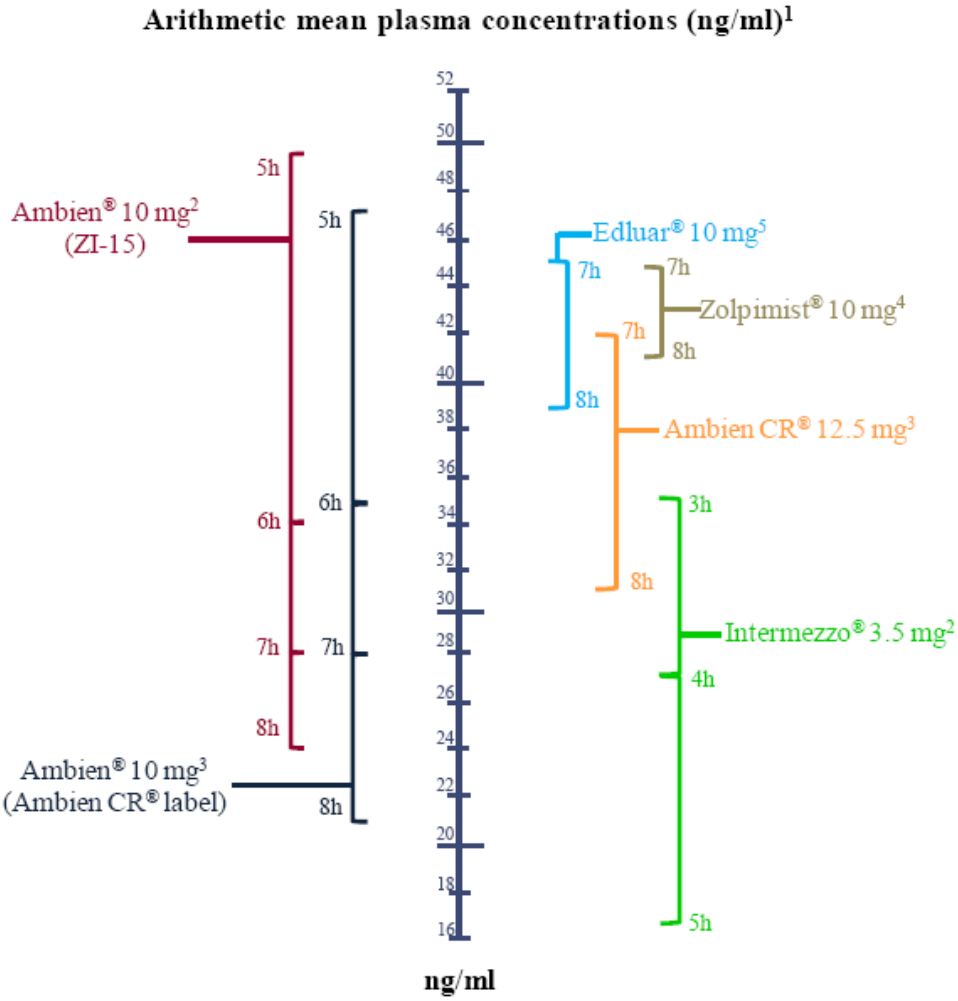
a) Driving Studies: The sponsor asserts the following from comparison of ZI-18 to published driving studies (based on SDLP):

- Intermezzo at 3 and 4 hours is less impairing than *incorrect* dosing (higher dose or taken closer to driving) of a variety of drugs, or correct dosing of flurazepam (Dalmane), an FDA-approved sedative-hypnotic.
- Intermezzo at 3 and 4 hours is *more* impairing than zaleplon (Sonata), either used as directed, or used at higher doses or closer to driving than recommended.

The sponsor concludes that driving impairment should not prevent approval of Intermezzo because Intermezzo presents less risk of impairment than the prevalent *incorrect* use of at least some sedative hypnotics, and because Intermezzo compares favorably to impairment caused by a number of drugs, most but not all of which are *not* approved for insomnia in the US.

b) Next-morning blood levels of other zolpidem products: The sponsor cites publicly available FDA Clinical Pharmacology reviews that found average blood levels of zolpidem from products used before bed (Edluar, Zolpimist, and Ambien CR) to be as high or higher, on average, than zolpidem levels 3 or 4 hours after Intermezzo (Figure 3). From this data the sponsor concludes that Intermezzo, even at 3 hours after dosing, would be safer for next-day driving than some FDA approved products even when those approved products were used as directed.

Figure 3: Average Zolpidem Levels from Approved Products Cited by Sponsor



CDTL Discussion:

a) Driving studies:

Cross-study comparisons are problematic to interpret because study conditions inevitably differ. In fact, a high degree of inter-study variation may exist in this type of study. For example, blood ethanol at 0.05% is often cited as

corresponding to an increase in SDLP of 2.5 cm, but Verster et al[2] recorded a change of only 1 cm. In addition, as noted above and by Dr. Massie, baseline SDLP differs greatly among studies, raising question as to validity of cross-study comparisons.

Even taken on-face, the sponsor's analyses are most convincing that Intermezzo is safer than incorrect use of other drugs, overlooking the critical fact that Intermezzo is also likely to be used incorrectly (albeit in somewhat different ways than drugs approved for before-bed use).

Evidence suggesting that other FDA approved sleep drugs like flurazepam may be impairing when used as directed does not diminish the need to demonstrate that Intermezzo is adequately safe.

b) Next-morning zolpidem levels from approved products:
The sponsor's argument is based on *average* blood levels from different products, but a major unaddressed concern for Intermezzo is impairment in patients at the high end of the distribution of blood levels.

The post-hoc cross-study comparisons made by the sponsor may not accurately reflect relative zolpidem levels after use of the various approved products. Zolpidem blood levels from Intermezzo show remarkable variability across studies. For example, in study ZI-13, blood levels at 4 hours after dosing were about 40 ng/ml for men, and 50 ng/ml for women, while in contrast, in study ZI-17, levels were about half that for men and women respectively. Similar variability appears to exist for zolpidem levels from other approved products (the Ambien clinical pharmacology review noted that zolpidem is a 'highly variable drug as indicated by the large degree of intersubject variation seen for its pharmacokinetics).

Finally, as noted above, evidence suggesting that other FDA approved sleep drugs may be impairing when used as directed does not diminish the need to demonstrate that Intermezzo is adequately safe.

6. Other Relevant Regulatory Issues

- CMC found the application, including the updated 4-element packaging system, was acceptable for approval.
- DMEPA notified the sponsor on 5/25/2011 that the proprietary name, Intermezzo, was acceptable if no other alterations were made.

[2] Verster, JC, et al., Residual Effects of Middle-of-the-Night Administration of Zaleplon and Zolpidem on Driving Ability, Memory Functions, and Psychomotor Performance. J. Clin Psychopharm 2002;6:576-83.

- CSS did not identify any issues that would preclude approval.

7. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response

- Risk Benefit Assessment

  The driving study and analysis of PK and PD data from other Intermezzo studies has *increased* concern about the risk of next-day impairment from Intermezzo.

  The new packaging and instructions adequately address the risk of inadvertent redosing in a single night, but morning blood levels of zolpidem, particularly in patients at the high end of range of exposures, remain a concern even when the drug is taken as directed.

  Evidence from the outpatient efficacy study suggests that some incidence of dosing with less than 4 hours of bedtime remaining is unavoidable. While any drug that induces sleep will impair driving if taken with too little time before driving, to be approved the drug should be safe enough so that relatively small dosing errors, including dosing 30- minutes, and perhaps even up to 60 minutes later than labeled, do not result in unacceptable risk of impaired next-day driving.

  Potentially, a lower dose formulation of zolpidem might still be effective for MOTN awakenings, yet not be associated with unacceptable risk of next-day impairment, as noted by Dr. Davis. Zolpidem exposure is higher in women than men, and potentially some dosing strategy that incorporates this fact would also help to mitigate risk of next-day impairment. Potential next steps the sponsor could take are described in more detail the 'Recommended Comments to Applicant' below.

- Recommended Comments to Applicant

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

In our Complete Response to the original NDA submission, we agreed that efficacy had been adequately demonstrated for Intermezzo. However, we found that you had not presented adequate evidence about the safety of residual morning levels of zolpidem from Intermezzo, particularly if patients inadvertently re-dosed Intermezzo in a single night, or inadvertently dosed with less than 4 hours of bedtime remaining. Both of these risks appeared potentially to be increased compared to other zolpidem products by the middle-of-the-night (MOTN)-dosing of Intermezzo.

We indicated in our Complete Response that it appeared necessary for you to demonstrate both that (a) Intermezzo, when taken as directed, did not unacceptably impair next-morning driving ability, and that (b) dosing errors could be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety could be shown to be acceptable.

We also stated in the CR letter that alternative packaging might help minimize the risk of dosing errors.

At the End-of-Review Meeting on January 20, 2010, you proposed alternative individual-dose packaging of Intermezzo that, on face, appeared to decrease concerns about risk of inadvertent re-dosing of Intermezzo. After full review of your current Complete Response, we agree that you have adequately mitigated this risk.

We remained concerned at the End-of Review Meeting that the alternative packaging you proposed might not adequately address the risk of impaired next-day driving from inadvertent dosing with less than 4 hours of bedtime remaining. We proposed that you might study the risk of dosing errors in a patient-use study prior to approval. However, you proposed conducting a study only of patient understanding of dosing instructions, arguing that a study that attempted to directly observe if patients actually followed dosing instructions would be neither possible nor useful, because patient behavior in the study would not be generalizable to actual clinical use. We agreed to consider your argument in your Complete Response.

After full review of your Complete Response, we agree with you that packaging and instructions clearly communicate that intermezzo must not be used with less than 4 hours of bedtime remaining. Importantly, however, we believe that this conclusion is consistent with the position that Intermezzo must still be shown to be safe in the context of ordinary, unavoidable deviations from labeled use. We agree with you that accurate measurement of such deviations is difficult because, for example, patients are more likely to dose correctly when under observation. We are still not convinced that a study of patient use is without value, as a high level of dosing errors would clearly be informative, but we would not compel you to conduct such a study. Instead, based in part on the deviations from dosing instructions that appear to have occurred in the

outpatient efficacy study (ZI-12) despite the highly controlled study conditions, we conclude that driving about 3.5 hours after dosing of Intermezzo should be considered as part of the safety review of Intermezzo.

During our review of your resubmission, we became concerned that patients at the high end of zolpidem exposure from Intermezzo would be at unacceptable risk of next-day impairment. We therefore asked you to conduct additional pharmacokinetic and pharmacodynamic analyses, which you submitted on May 26, 2011 (Amendment 40). In one analysis, you identified patients in each PK study that were in the highest 10th percentile for exposure (based on Cmax, AUC, and zolpidem blood level at 4 hours post-dosing). Out of 25 patients you identified, at 4 hours after Intermezzo 3.5 mg, 14 had a blood level above 40 ng/ml, 7 had a level above 60 ng/ml, and one had a blood level of ≈ 80 ng/ml. Several types of evidence from your development program suggest that such levels are likely to result in clinically important driving impairment. Zolpidem blood levels in the driving study (ZI-18) were not measured, but zolpidem blood levels from the PK studies suggest that the average zolpidem level in the 3-hour arm of the driving study was unlikely to be greater than ≈30- to 40 ng/ml. The 3-hour arm was positive in the symmetry analysis up to and including the 4 cm SDLP threshold, suggesting clinically meaningful impairment of driving in this range of zolpidem blood levels. It might be hypothesized that the impaired subjects in the driving study at 3 hours where those who had above-average blood levels (i.e. blood levels > 40- or even 50 ng/ml) but even if the signal for impairment was driven largely by patients with such levels, as noted above, such levels commonly occur 4 hours after Intermezzo dosing.

Additional concern arises from the fact that patients at the high end of the distribution have blood levels about the same as what was likely the average Cmax from Intermezzo 3.5 mg in the efficacy studies (PK was not measured in the efficacy studies). This blood level was, of course, shown to decrease MOTN sleep latency, and there is concern that a similar effect in the morning would increase the risk of falling asleep while driving. Moreover, these blood levels are double or more the likely average Cmax from 1.75 mg Intermezzo, a dose also that showed a statistically significant decrease in sleep latency (study ZI-06-010). Our concern about morning levels of zolpidem increasing the risk of falling asleep while driving is supported by the fact that such an event occurred in the driving study.

In your Complete Response, particularly your May 26, 2011 amendment, you argued that the morning blood levels described above do not impair driving. You base this conclusion largely on the fact that there was little correlation between zolpidem blood levels and some of the pharmacodynamic responses you measured, such as Digit Symbol Substitution Test (DSST). However, as we stated in our Complete Response to your original submission, we do not believe that measures such as DSST or patient questionnaires adequately address possible adverse effects of zolpidem on driving ability. In contrast,

while the driving study did not examine different doses of Intermezzo, and acute tolerance could have affected pharmacodynamic response in relationship to time from dosing, the results suggest that higher blood levels of zolpidem (at earlier time points) are positively correlated with greater impairment of driving. More fundamentally, dose-response studies of zolpidem, including your inpatient efficacy study (ZI-06-010), appear to leave little doubt that pharmacodynamic response to zolpidem increases with dose in the range in question.

In your Complete Response, you provide a number of additional arguments in support of the safety of Intermezzo. However, we similarly do not find these arguments compelling.

You argue that Intermezzo is safer than other FDA-approved drugs for insomnia. Such arguments are fundamentally problematic in terms of both evidence and regulatory requirements; there appears to be no actual data supporting your claims, and evidence you present raising concern that other FDA-approved sleep drugs may be impairing does not diminish the regulatory requirement to demonstrate that Intermezzo is adequately safe. That said, we have considered your argument that the safety of currently approved drugs, including risk from misuse, can help in understanding the acceptability of risk from a new drug.

You assert that next-day impairment from Intermezzo will be much less than risk from off-label, MOTN use of drugs approved for before-bed use. However, your conclusions are based on selective premises. For example, the potential for off-label use of Intermezzo is not acknowledged, and it is far from clear that off-label use of Intermezzo will be any less frequent, or of less serious consequence, than off-label use of insomnia drugs intended for before-bed use. Similarly, you conclusions don't fully consider, or propose how to address the fact that off-label MOTN use of some insomnia drugs (e.g. zaleplon) might be safer than off-label, or potentially even as-labeled use of Intermezzo.

Another comparative safety argument you present is based on *average* blood levels in the morning after use of various zolpidem products. You assert that residual levels from Intermezzo are no higher than residual levels from currently approved products. Your argument, however, does not consider the *range* of morning blood levels from these products; as discussed above, patients at the high end of exposure from Intermezzo are of particular safety concern. Also, your argument is based on cross-study comparisons, which are generally unreliable, particularly in the case of zolpidem, given the high degree of variability seen across PK studies.

For the above reasons, therefore, we can not conclude that you have adequately demonstrated that Intermezzo is safe.

We believe that a necessary first step in addressing our concerns about residual morning levels of zolpidem from Intermezzo would be a more thorough characterization of the distribution of blood levels that can occur the morning after dosing. While you have conducted a number of pharmacokinetic studies, we are concerned that the subjects in these studies may have been too homogenous to fully represent blood levels in the broader U.S. population. For example, while we acknowledge that the effect of race on zolpidem blood levels is not well-characterized, at least one published report suggests that race has a relatively large effect on zolpidem blood levels (Salva, P. and Costa, J., Clin Pharmacokinet 29, 1995). It is also not clear to us that the effect of body weight/composition on zolpidem pharmacokinetics has been adequately characterized.

While we don't exclude the possibility that you could present convincing evidence that the zolpidem blood levels from Intermezzo are safe, we don't believe this is likely. Therefore we would recommend as a second step that you 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.).

Finally, depending on the residual zolpidem levels that might result after mitigation strategies are implemented, it might be necessary for you to demonstrate, in an adequately powered study with demonstrated assay sensitivity, that the levels still present do not present an unacceptable risk of next-day impairment. This might be accomplished with a study generally similar to your current driving study, although we would be open to proposals for other types of studies.

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

/s/

RONALD H FARKAS
07/12/2011

RUSSELL G KATZ
07/20/2011
I agree with Dr. Farkas's conclusions-see my separate memo.

MEMORANDUM

DATE: July 14, 2011

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 23-328/S0036

SUBJECT: Action Memo for NDA 23-328/S0036, for the use of Intermezzo (zolpidem tartrate sublingual) 1.75 mg and 3.5 mg, to treat insomnia following middle of the night (MOTN) awakening

NDA 23-328/S0036, for the use of Intermezzo (zolpidem tartrate sublingual) 1.75 mg and 3.5 mg, to treat insomnia following middle of the night (MOTN) awakening, was submitted by Transcept Pharmaceuticals, Inc., on 9/30/08. Intermezzo is to be given at night to help patients who have awoken and have difficulty falling back to sleep. It is to be taken once, and only when the patient has at least 4 hours more sleep time. The division issued a Complete Response (CR) letter on 10/28/09.

The CR letter noted that the division had concluded that the sponsor had submitted substantial evidence of effectiveness for Intermezzo for MOTN awakening. However, the division had numerous concerns about the safety in use of the product. Specifically, the letter noted that there was reason to believe that blood levels of zolpidem would potentially be high enough 4 hours after dosing to pose a significant safety risk.

In particular, the division noted that mean plasma levels 4 hours after dosing were likely to be about 25 ng/mL. Similar zolpidem plasma levels had been reported to occur about 5-6 hours after a 10 mg dose of oral zolpidem, and were associated with impaired driving. This strongly suggested that many patients would be at risk of being impaired while driving the morning after taking Intermezzo, even if it had been taken correctly with 4 hours left of sleep.

Further, the division had expressed concern that there was a significant risk that patients would take the drug with less than 4 hours left of sleep, posing an even greater risk of being impaired while driving. This concern was further enhanced by the observation that about 3% of patients did so in the clinical trials, despite the fact that they had to call a central number when they woke up and receive permission to take the pill (predicated on their having at least 4 hours of sleep left) and were told that they must not take the pill.

In addition, we were concerned that some patients might take more than one dose in the middle of the night, given that the proposed packaging contained 10 pills and was to be kept at the bedside and patients may not remember that they

had taken a pill already. This concern was also increased by indirect evidence (based on the number of pills patients returned at visits) that patients in the clinical trials took more pills than they were supposed to have taken.

The sponsor had proposed several maneuvers to mitigate any risk of dosing errors, including a Medication Guide, a Risk Evaluation and Mitigation Strategy (REMS), pharmacovigilance measures, and a Phase 4 study to evaluate any risks of the sorts we were concerned about. The division found that none of these proposals would adequately assure that patients would not make dosing errors.

In the letter, we had proposed that the sponsor obtain additional data on the effects, if any, the next morning on driving, and also that they propose additional ways to minimize dosing errors, including alternative packaging.

Subsequent to the issuance of the CR letter, the division met several times with the company and its consultants to discuss the various issues noted in the CR letter. In particular, meetings were held on 1/20/10 (at which alternative packaging was discussed) and 3/24/10 (at which the design of a study to assess the effects of Intermezzo on next-day driving was discussed; at that time, we agreed that the sponsor's proposed study was acceptable in design).

The sponsor submitted a Complete Response to the CR letter on 1/14/11. This response has been reviewed by Dr. Carole Davis, medical reviewer, Dr. Tristan Massie, statistician, Dr. Jagen Parepally, Office of Clinical Pharmacology, Dr. Loretta Holmes, Division of Medication Errors and Analysis (DMEPA), Robin Duer, Division of Risk Management (DRISK), Dr. Lyudmila Soldatova, chemist, and Dr. Ronald Farkas, neurology team leader. The clinical team recommends that the application not be approved at this time, and that the division issue a second CR letter.

The submission contains the results of a driving study, and additional pharmacokinetic data. Much of the latter data were submitted on 5/26/11, in response to requests from the division for additional data addressing the effects of sex and body weight on the kinetics of the product. In addition, the sponsor has proposed alternative packaging.

Dosing Errors

In response to the division's concerns about potential dosing errors, the sponsor has proposed a "Unit Dose Pouch" which contains a single Intermezzo pill that is to be kept by the patient's bedside, as well as instructions for use. Once the patient takes the pill, the empty pouch remains at the bedside; in this way, the patient is reminded that the pill has been taken if they wake up later and consider taking another pill, and to take an additional pill would require the patient to get out of bed and retrieve another pill. For these reasons, the sponsor concludes that the risk of taking an additional pill is minimized. The sponsor also conducted

a labeling comprehension study that they conclude demonstrates that patients will understand the appropriate way to manage this potential problem.

Regarding the possibility that patients will take the pill with less than 4 hours left of sleep, the sponsor proposes that the labeling and new packaging will help minimize this risk as well. In addition, the sponsor has provided a "dosing wheel" that the patient can set prior to going to sleep that will display the latest time at night that the patient can take a pill (the patient dials in the time that they need to wake up, and the wheel displays the time that is 4 hours prior to that time).

The division had previously discussed with the sponsor performing a study to determine the incidence of dosing too late in the night. In the submission, the sponsor asserts that an informative study of this kind could not be done (primarily because the conditions of such a study would sufficiently affect patients' behavior to the point that it would preclude an accurate assessment of how they would behave in the real world), and further that such a study is unnecessary, because: 1) Intermezzo is safe even if taken 3 hours prior to getting out of bed, 2) zolpidem levels at 3 hours after Intermezzo are no greater than zolpidem levels 7 hours after other approved zolpidem products, 3) misdosing Intermezzo is "safer" than misdosing other zolpidem products, which is known to occur not infrequently, 4) the proposed packaging and labeling would adequately minimize the risks, and 5) patients would be able to tell that they are impaired the next morning and, therefore, not engage in dangerous behaviors.

Driving Study

As noted above, the sponsor has submitted the results of a driving study, the design of which we had agreed was acceptable.

Briefly, the study assessed the effects of Intermezzo 3.5 mg at 3 or 4 hours after dosing. Because driving was assessed at 3 or 4 hours after dosing, patients were actually awoken 2.25 or 3.25 hours after dosing (that is, 45 minutes before they were tested). Each driving assessment was 1 hour long.

The study was a 4 way cross-over trial, in which 20 men and 20 women were tested under 4 conditions (3 hours after dosing, 4 hours after dosing, placebo, and Zopiclone 7.5 mg, tested 7 hours after dosing, as a positive control). The study was performed using on-road driving, with the primary outcome being the standard deviation of lateral position (SDLP). In this methodology, patients are instructed to maintain a constant position relative to the left boundary of the lane.

As described by Dr. Farkas, the primary analysis was a so-called "symmetry analysis". In this analysis, the proportion of patients who had a worsened SDLP of a given degree was compared to the proportion of patients who had an improved SDLP of that same degree. The primary threshold for a meaningful change in SDLP was 2.5 cm (or greater), which is the degree of SDLP that

presumably, on average, is seen in subjects with a blood alcohol level of 0.05%, a level considered to be a risk factor for car crashes.

As described by Dr. Farkas, 3 subjects discontinued the study early because they fell asleep during the testing: 2 on zopiclone, and one in the Intermezzo 3 hour group, at 3 hours, 44 minutes after dosing. The Intermezzo patient was a 23 year old woman who was 53 kg; she was the lightest subject in the study.

The sponsor acknowledges that there was a statistically significant impairment of driving in the 3 hour post-dosing group up to (and including) the 4 cm SDLP mark. With regard to the 4 hour post dosing group, there were no statistically significant effects at the prospectively defined thresholds. However, as displayed in Dr. Farkas's Table 1, it is clear that, starting at an SDLP of 1.75 cm, there are more patients who were impaired than were improved at every threshold up to, and including, 4 cm, though the vast majority of patients were considered "neutral", and the number of patients that were worse decreased with increasing SDLP threshold (for example, at 1.75 cm, 8 were impaired and 3 were improved; at 2.5 cm, 5 were impaired and 1 was improved; at 4 cm, 1 was impaired and none were improved).

The results for the zopiclone treatment arm demonstrated a clear effect on all measures of driving impairment that was greater than that seen with either the 3 or 4 hour Intermezzo conditions (see, for example, Dr. Davis's Appendix Table 3).

Plasma levels the next morning

As noted above, the division asked the sponsor to submit detailed analyses of plasma levels at various time points after dosing. These data, reviewed, in detail by Drs. Parepally and Farkas, yield important findings.

In particular, the data taken as a whole, demonstrate that, for any given dose, women have higher plasma levels of zolpidem than men: estimates range from about 50% to about 70% higher in women than men, though a few studies showed no differences. The data do not establish any significant (or clear) effect of weight on plasma levels. Some data also suggest that women are more sensitive to the effects of any given plasma level of zolpidem than men are; (see, for example, Dr. Farkas's Figure 1, which displays the results of DSST testing for men and women by plasma levels).

Dr. Parepally examined zolpidem levels at various times after dosing, as seen in numerous pharmacokinetic studies. Dr. Farkas's Table 2 displays the results of this examination. Briefly, this table makes clear that significant numbers of patients can have relatively high zolpidem plasma levels up to 5 hours after a 3.5 mg dose; in general, more women have higher levels at any given time point.

For example, in one study (Study 16), 17/20 women had levels >30 ng/mL at 3

hours after dosing, and 10/20 women had levels >30 ng/mL at 5 hours after dosing. In this same study, 5/20 women had levels >50 ng/mL at 5 hours after dosing, and 3/20 women had levels >60 ng/mL 4 hours after dosing.

At the request of the division, the sponsor also examined, in each PK study, the patients in the highest 10th percentile of plasma levels. They identified a total of 25 subjects; out of these 25, 14 had a plasma level >40 ng/mL 4 hours after a 3.5 mg dose, 7 had a plasma level >60 ng/mL, and one had a plasma level of about 80 ng/mL. As described by Dr. Farkas, plasma levels of about 55-65 ng/mL were associated with significant changes on the DSST in women in Study 009 (see his Figure 1). As he also notes, in other studies no differences in impairment between men and women on the DSST were seen (despite the fact that women again had higher plasma levels than men). In one of these studies, however, no impairment was seen at 1 hour, a time after dosing at which impairment would be expected; this raises the question of whether or not the study was adequate (i.e., it had no assay sensitivity).

As noted by Dr. Farkas, the ***highest*** zolpidem plasma levels seen at 4 hours post dosing were likely to have been about the same as the ***average*** Cmax with the 3.5 mg dose, a plasma level clearly associated with profound CNS depression (given that it is effective in producing sleep). Further, as Dr. Farkas notes, these 4 hour levels were ***clearly greater*** than the average Cmax seen with the 1.75 mg dose, a dose also shown to be effective at producing sleep.

The sponsor has presented data that the average zolpidem plasma levels 4 hours after dosing with Intermezzo are comparable to the average plasma levels the next morning with other approved zolpidem products (Edular, Zolpimist, Ambien, Ambien CR) when these products are taken before bed (that is, as labeled).

For example, according to the sponsor, average plasma levels of zolpidem after taking the various products at the appropriate times are as follows:

Drug	**Avg zolpidem level (ng/mL) X hours after dosing**				
Hours after dosing	**3**	**4**	**6**	**7**	**8**
Ambien 10 mg			34	28	21-24
Ambien CR 12.5 mg				42	31
Edular 10 mg				45	39
Intermezzo 3.5 mg	35	27			

Conclusions

Taken as a whole, the sponsor concludes that the steps they have taken (new product packaging, labeling) will adequately minimize the risk of dosing errors. They further argue that performing a specific study to examine the question of whether or not dosing errors will occur (a suggestion made by the division) is both not feasible and unnecessary.

Further, and critically, they also have concluded that MOTN dosing with Intermezzo 3.5 mg results in no clinically meaningful deleterious effect on driving 4 hours after dosing. For these reasons, then, the sponsor concludes that Intermezzo can be used safely, and should be approved.

Regarding the issue of potential dosing errors, I agree that the sponsor's proposal to package the product in single pill pouches would be expected to minimize, to the extent possible, the risk of patients taking multiple pills in a given night. Of course, it will be possible for patients to place more than one pouch at the bedside before going to sleep, as it will be possible for patients to get up in the middle of the night, get out of bed, and retrieve a second (or third) pill from wherever they store the medication. However, I believe that the re-packaging, and patient labeling, will reduce this possibility to an acceptable minimum.

The sponsor also concludes that there is a minimal risk of patients taking the drug with less than 4 hours left of sleep, and, even if they take the medication with only 3 hours left of sleep, this is not unacceptably dangerous.

With regard to the question of whether or not patients can reliably take the drug with at least 4 hours of sleep left, I believe it is fair to say that we already know that at least some patients will dose inappropriately late in the night, based on the fact that a small, but not ignorable number of patients did so under the controlled conditions of the clinical trial, even when they were told, ***at the time they awoke***, that they should not do so. It is reasonable to assume that, under real life, unmonitored conditions, the number of patients who will do so will be greater still than the number who did so in the clinical trials. Further, although I think the "dosing wheel" that the sponsor has produced is potentially useful, I do not believe that we can be confident that it will reduce such errors to an acceptable degree (for example, if a patient wakes up 3:30 AM, and sees, by the wheel, that they should not take the pill after 3 AM, it is not at all clear that many patients will not take the pill). It is impossible to know, of course, in what sort of "window" around the permitted time individual patients will consider dosing to be acceptable, but it is reasonable to assume that such a window will exist for at least some patients. In any event, we have no evidence that such an approach will not be taken by (many?) patients. I am inclined to agree with Dr. Farkas that another more formal study of this question is not likely to shed useful light on this problem.

For these reasons, I agree with the review team that the our consideration of the safety in use of Intermezzo must take into account the view that patients will dose themselves later in the night than they should. Of course, we must also consider the safety in use when patients dose correctly according to the proposed labeling (that is, with 4 hours left to sleep). It is obviously true that the proposed labeling also anticipates that many patients will take the drug more than 4 hours before their wake time. However, we have to give primary consideration to the safety in use at the limit of the timing of the dosing that will be permitted in the label (i.e., with 4 hours of sleep remaining).

The sponsor's primary arguments supporting their conclusion that Intermezzo can be used safely are based on the findings from the driving study, which in their view support the safety 4 hours after dosing, and their analyses of the pharmacokinetic data which, again in their view, suggest that levels at 4 hours after dosing are not associated with the potential for adverse events. In addition, they assert that even if the drug is taken with only 3 hours of sleep time left, it is still safe, and that, in any event, this will still be safer than other approved drugs when they are taken inappropriately (that is, for example, when they are taken in the middle of the night, a form of inappropriate dosing that is known to occur with these other drugs).

It is true that the primary analysis of the driving study did not detect statistically significant impairment, as measured by SDLP at 4 hours after dosing. However, as Dr. Farkas describes, there were nominally significant findings for thresholds smaller than the primary threshold of 2.5 cm of SDLP (a finding of uncertain, but not obviously irrelevant, clinical significance), and there is evidence of numerical, if not statistically significant, impairment at levels of SDLP even greater than 2.5 cm.

The sponsor claims that, although the times assessed in the driving study were nominally at 3 and 4 hours after dosing, in reality the testing was done at 2.25 and 3.25 hours after dosing. It is true that this was when testing began; however, patients drove for 1 hour, so that the test in actuality assessed patients from 2.25-3.25 and 3.25 to 4.25 hours after dosing, durations that are clearly relevant to the question of what the effects on driving would be in the morning if the patient took the pill at 3-4 hours prior to getting out of bed. Indeed, one patient fell asleep at 3 hours 44 minutes after dosing. The sponsor argues that this is likely not related to the treatment because plasma levels were higher at 3 hours and she did not fall asleep then. I agree that it is impossible to know for certain that the drug was responsible for her falling asleep, but the fact that it happened at a point when the zolpidem plasma levels were not at their highest in no way argues, in my view, against the possibility that the drug was responsible (for example, we do not know what the exact temporal relationship might be between plasma levels and pharmacodynamic effects).

It is also worth noting that there was a statistically significant difference in the mean SDLP at 4 hours compared to placebo (0.8 cm; p=0.02) and in the standard deviation of speed (SDS; p=0.01). The estimates of the effects in these cases are quite small and are, at worst, of uncertain clinical meaning. Nonetheless, they are consistent with the view that Intermezzo can produce, on average, detectable deleterious pharmacodynamic effects.

Of more importance, however, is the identification of substantial numbers of patients who have plasma zolpidem levels that are considered to be associated with significant impairment.

As described earlier, numerous analyses of various pharmacokinetic studies revealed a not inconsiderable number of subjects with plasma levels at 4 hours after dosing of 40 ng/mL and greater. The clinical impairment that such levels can produce is not known with certainty, and, clearly, the relationship between plasma levels and performance varies among individuals. Nonetheless, evidence from some of the studies examined here, as well as evidence discussed in the division's reviews of the initial submission (for example, data in the literature, previously reviewed and discussed, suggest that a zolpidem plasma level of 25 ng/mL is associated with impaired driving) strongly suggest that levels of greater than even 30 ng/mL can be dangerous. Of course, levels 3 hours after dosing will be that much greater (indeed, the results of the driving study at 3 hours after dosing support this conclusion, and also support the conclusion that the mean levels of about 35 ng/mL seen at 3 hours are clearly associated with impairment). And as noted by Dr. Farkas, some patients' 4 hour plasma levels are likely to be similar to the mean Cmax at the 3.5 mg dose, clearly a level that has been shown to induce sleep. In addition, many patients will have levels at 4 hours that are greater than those seen at the Cmax for the 1.75 mg dose, also a dose known to induce sleep. It is also very clear that women have greater levels for a given dose of Intermezzo than men; it does not appear that this is primarily related to body size. Some data (though not definitive) also suggests that women may be more sensitive to the effects of a given level of zolpidem than men.

The sponsor argues that the plasma levels seen at 4 hours after dosing with Intermezzo are similar to, if not less than, those seen in the morning after approved zolpidem products, taken as directed (i.e., before going to bed). Although this may be true, this observation does not address the question of those patients with levels greater than the average value; we have seen that there are considerable numbers of such patients. The sponsor has provided no evidence that the spread of plasma levels seen with Intermezzo is comparable to that with other approved zolpidem products. Without these comparative data, we cannot know how to compare these products.

It is worth noting that all of this would be less problematic if patients could reliably recognize that they were impaired. In such a case, patients would know that they

were impaired, and would be in a position to assess whether or not they should engage in dangerous activities, like driving. However, it is widely acknowledged that there is no reliable symptom that patients can recognize that would allow them to know that they are impaired.

It is also worth noting that, even if there were such a symptom, there would still be a problem. Driving to work in the morning is such a universal activity, and of such importance to so many people, that it is easy to imagine that patients would still engage in this behavior, ***even if they knew they were impaired***.

The sponsor makes numerous such comparative statements to support the safety, and therefore the approval, of Intermezzo (e.g., the plasma levels are the same in the morning, the results of the driving study showed smaller effects than studies of other approved products).

It is difficult to interpret these statements definitively.

For example, as stated above, we have no information about the variability in plasma levels among these products, and the conditions in the various driving studies make comparisons difficult.

I also believe that the nature of this product will likely predispose to patients taking the drug later in the night than recommended. It is, of course, true that any drug can be taken at the wrong time. But it is relatively easy to take a typical hypnotic at the right time; i.e., just prior to going to sleep. Taking Intermezzo at the right time, though, can be more problematic, given the middle of the night nature of dosing. One can easily imagine, even if patients consult the "dosing wheel" when they wake up, that patients will permit themselves a "window" around the 4 hour mark they are not supposed to dose beyond. Further, it is not hard to imagine that many patients will simply not check to see what time it is when they wake up, despite labeling and patient education. Indeed, as has been noted, patients took drug inappropriately in the highly controlled conditions of the clinical trials, even when they were told not too. These concerns, coupled with the plasma level data discussed above, raise serious questions about the safety in use of Intermezzo.

The sponsor asserts that Intermezzo (taken correctly) is less dangerous than misuse of approved hypnotics, and they document that there is considerable such misuse. This may be true, and it is clearly problematic if, for example, patients take approved doses of hypnotics in the middle of the night off label. However, I do not believe that we should approve a drug that we have concluded is not safe in use simply because it is safer (presumably) than approved drugs taken inappropriately. I believe there are other ways to address this problem.

As discussed above, the sponsor has identified numerous subjects who have morning plasma zolpidem levels at 4 hours after dosing with Intermezzo that can

be associated with functional impairment. It is fair to ask what how many impaired patients (with what degree of impairment) would preclude approval of such a product.

There is no obvious right answer to this question, though in searching for an answer, the same considerations should be brought to bear that are ordinarily considered when contemplating a drug that causes a significant risk. Although it is difficult to designate a specific number, in my view, the number of patients seen in this application to have sufficiently high morning plasma levels in the relatively small numbers of patients in whom we have appropriately timed plasma level data is sufficient to raise fundamental questions about the potential deleterious effects on the public health were Intermezzo to be approved and used by many people.

What if the sponsor is correct (although at this time we do not know if they are), that the risk (whatever it is) with Intermezzo is similar to that of the approved products? Although, as I noted above, we do not have information about the spread of plasma levels with the approved products, we have seen that a mean zolpidem plasma level of about 35 ng/mL at 3 hours after dosing is associated with impairment (although plasma levels were not taken in the driving study; these levels were taken in other studies).

The question is a fair one. If we were confident that Intermezzo posed no additional risk compared to approved products, I suppose there is an argument to be made that adding another zolpidem product to the marketplace poses no additional risk. Indeed, because Intermezzo is taken only when needed, and not every night (as presumably the current drugs are), one could argue that approving this product would produce a net public health benefit, because less drug overall would be used.

Although this is a somewhat attractive argument, I believe that it is potentially flawed, primarily because we have no good way of knowing, a priori, whether approving Intermezzo under these assumptions would be a net benefit or not. For example, if Intermezzo is frequently used inappropriately, it might result in a net harm to the public health if it replaced (to a significant extent) other already marketed drugs. Further, there are serious questions about the propriety of approving a drug we have concluded is not acceptably safe, even if other drugs are already available that might be equally unsafe. Finally, as noted above, we do not have evidence that it does not pose an additional risk compared to marketed zolpidem products, even if it is taken correctly.

In sum, then, the sponsor has adequately addressed the possibility that patients might take more than one pill in any given night. I do not believe, though, that they have adequately minimized the possibility that patients may take the pill with no more than 4 hours of bedtime remaining. For this reason, we must consider the possible negative next day effects of taking the medication with, for example,

only 3 hours of bedtime remaining. I also do not believe that patients can reliably determine if they are impaired in the morning.

Given these concerns, the following observations support the view that the sponsor has not demonstrated the safety in use of Intermezzo.

The results of the driving study demonstrate that patients are impaired when driving between 2.25 and 3.25 hours after dosing. There is also evidence that patients may be impaired when driving between 3.25 and 4.25 hours after dosing. Further, and critically, a substantial number of patients will have zolpidem plasma levels that are sufficiently high to raise concerns about their ability to function (i.e., drive) at 4-6 hours after dosing. The lack of a statistically significant effect at 4 hours on the driving test does not undermine the conclusion that patients with high levels may be impaired at and beyond 4 hours after dosing. Recall that only 20 subjects were tested in each arm of the study; that is, only 20 subjects were tested 4 hours after dosing. It would not be unexpected to not have encountered any patients with the higher levels in such a small cohort. Even if several subjects did have higher levels, it would not necessarily be unexpected that they did not have impairment, although, it must be pointed out, it is also possible that they ***did*** have impairment (recall that some patients were impaired at 4 hours, and that plasma levels were not taken in the driving study, so that we really cannot correlate high levels with performance).

Given that there is reason to believe that a not inconsiderable number of patients may be impaired at 4 hours after dosing, that patients cannot reliably determine if they are impaired, that the nature of the product and the MOTN dosing will result, in my view, in numerous patients taking the drug with less than 4 hours of sleep remaining, and that driving in close temporal relation to wakening is very common, I conclude that the sponsor has not demonstrated that Intermezzo can be used acceptably safely according to proposed labeling. For these reasons, then, I will issue the attached Complete Response letter.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
07/14/2011

NDA #	22-328
Applicant	Transcept Pharmaceuticals, Inc
Type of Submission	Complete Response review
Date of Submission	January 14, 2011
PDUFA Goal Date	July 14, 2011
Date Completed	June 24, 2011
Clinical Reviewer	Carole L. Davis, D.O., M.P.H. Division of Neurology Products
Proprietary Name	Intermezzo
Established Name	Zolpidem tartrate sublingual tablet
Dosage forms / Strength	3.5 mg and 1.75 mg sublingual tablets
Proposed Indication(s)	Treatment of middle-of-the-night insomnia
Population	Adults

1. Executive Summary

If approved, Intermezzo, zolpidem tartrate sublingual tablets (3.5 mg for adults, 1.75 mg for elderly), would be the first insomnia medication for the indication of middle-of-the-night (MOTN) insomnia. The pivotal trials, and earlier phase trials, evidenced efficacy for both dosage strengths (although the 1.75 mg dosage was included in only one of the two pivotal trials), and in general the safety review was unremarkable except for the lack of thorough testing for possible residual next-day effects in higher-level functioning. At the end of the NDA review cycle, concerns remained on several issues, and a Complete Response (CR) letter was sent to the sponsor, Transcept Pharmaceuticals, Inc.

The dose strength of Intermezzo at 3.5 mg is considerably lower than the reference drug, Ambien® 10 mg. However, the plasma concentration at 4 hours (26.69 ng/mL) remains slightly higher than the Ambien® at 8 hours (23.76 ng/mL), and there was gender discrepancy, with higher PK levels seen in female subjects. It was not clear whether these were within an acceptable risk/benefit ratio, or whether they potentially posed additional risks.

The MOTN dosing with a medication likely to be kept at the bedside posed a special set of concerns. (b) (4) As a result, the Agency requested the sponsor to provide assurances that only appropriate MOTN dosing would occur, and that early morning functioning would be safe.

In the Complete Response, the sponsor provided a complete repacking design to insure use of only a single tablet per night, a timing-wheel for dosing and expanded packaging and labeling instructions to minimize risk of dosing with too little bedtime remaining, and trial results for ZI-18, a highway driving trial. The cross-over trial was designed with treatment arms to commence driving at exactly 4 hours, and 3 hours post Intermezzo dosing, for comparison to the placebo and zopiclone (9 hours post-dosing) arms.

The repackaging as individually packaged tablets is excellent, and should solve the risk of inadvertently re-dosing. The increased late-dosing cautions and timing-wheel are probably as adequate as can be achieved. They are acceptable, and should solve the problem if patients use the medication as instructed. Purposefully dosing too close to morning activities remains a risk, as with any sedative-hypnotics. If used as directed, it is unlikely that driving would be done immediately upon awakening without any time for morning activities, such as showering and dressing, providing time for PK levels to decrease before picking up the car keys. Even more problematic is the possibility of purposeful dosing with too little bedtime remaining. For example, an insomniac awake at ~4 a.m. might medicate to "catch a few hours of sleep", even if setting the alarm-clock for 6:30 a.m. Undoubtedly late-dosing is already occurring with sleep-aid medication dosages meant only for bedtime use. However, we have no way of assessing comparative risk, and probably neither is acceptably safe.

The driving trial, ZI-18, used a Standard Deviation of Lateral Sway (SDLP) with commonly used, but never validated, threshold of 2.5 cm. In the cross-over driving testing, the SDLP threshold (t*) evaluations use the SDLP on drug treatment arm driving minus the SDLP on placebo arm driving. At the designated threshold for the primary endpoint, t*>2.5 cm, 5 of 40 of the enrolled subjects (12.5%) would be designated "impaired drivers" at 4 hour post-dosing in the treatment arm of Intermezzo. One of the 40 subjects (2.5%) recorded a SDLP change of 6.5 cm. which suggests a level of impairment that might be slow in resolving. If driving at 3 hours post-dosing, 10 of the 40 subjects (25%) exceeded the >2.5 cm SDLP change threshold, including 2 subjects (5%) at t*= >5.0 cm, and one (2.5%) with an SDLP change of 6.6 cm.

The driving trial was well-designed and conducted, but failed to resolve questions regarding which patients might potentially be at increased risk, and which PK levels or demographic variables might aid in their identification.

The sponsor was requested to cull any available pharmacokinetic (PK) or pharmaco-dynamic (PD) data from all the Intermezzo drug development trials for review. The request was a large undertaking late into the review cycle, but the sponsor complied furnishing data from 3 PK trials, and 3 PK/PD trials.

The Transcept review and summary, focused on evaluation of the "top 10^{th} percentile" individuals for pharmacokinetic and pharmacodynamic changes (i.e., the high responders). The Sponsor states that the "top 10^{th} percentile" individuals do not represent an evaluation of "outliers" but are instead components of the expected between-subject variability, individuals at one end of an expected distribution. The generalization is more logical for statistical than clinical analyses. Even when seen from the perspective of an expected distribution, it is still important to localize what the upper end of the distribution represents. In this case it is the same plasma concentration levels of zolpidem at 4 hours post-dosing (early morning) which had consistently been shown to be effectively sedating at 20 minutes post-dosing, or significant levels of change on next-morning PD tests.

Overall, this clinical review reaches the same conclusion as the sponsor that elevated PK levels at 4 hours post-dosing with Intermezzo 3.5 mg do not appear to have a direct correlation with decreased PD functioning, based on the data available. The conclusion could lead to the assumption that females are not at increased risk despite higher blood plasma levels and slower drug clearance (t½). However, the validity of that assumption is difficult to determine. A major problem is the type of testing used for pharmaco-dynamic assessments.

The Digital Symbol Substitution Test (DSST) routinely used for PD assessments in insomnia medication trials is quite inadequate to provide the reassurance, as discussed further in the body of this review. The other assessments used, such as Choice Reaction Time (CRT), have the same short-comings, and are less validated for trials. The fault is not with the sponsor, or their drug development program, which completed all the requested product development components, but was reviewed with recently gained insight into potential safety concerns with this class of drugs. The reference drug Ambien® 10 mg has not been evaluated at the same standards, so comparisons cannot be made. The sponsor may be quite correct, that the very elevated PK levels in some individuals at 4 hours post-dosing is an expected variant. The levels may reflect increased sensitivity due to genetic or metabolic differences yet undetermined. However, the zolpidem plasma concentration levels in some of the female subjects at 4 hours post-dosing (C_4) were higher than the mean C_{max} (usually at ~ 45 minutes) for the male population in nearly all of the trials. Since the PD assessments done within the first hour post-dosing indicated statistically significant evidence of sedating effectiveness, the concern remains that the very elevated C4 levels in the female "outliers" may adversely affect early- morning functioning.

Gender discrepancy in the pharmacokinetics of the hypnotic medications, including the reference drug Ambien®, has been noted in other trials (Greenblatt DJ, et al. 2000). Sponsor acknowledges that women have up to 50% higher systemic exposure (based on AUC) then men, and the difference is only partly explained by body weight. With the current review, the only sensitive PD assessment is the driving trial, where since PK testing was not included in the trial, direct comparisons cannot be made. So, the concern remains that the elevated plasma levels may have significance, and one small-population driving test, without concomitant PK testing, doesn't furnish enough reassurance regarding the dosage strength choice for Intermezzo.

Intermezzo would be a good addition to the medications available for insomnia. Currently patients with middle-of-the-night insomnia have the choice of treating in a prophylactic fashion at bedtime, when medication might not actually be needed that night, or treating in the middle of the night, usually with a medication developed for a 7 to 8 hour sleep period before active functioning. Zolpidem is a major component of the sleep-aid market, and will continue to be used. Having a low-dose, indication-targeted formulation available for consumers, would be an improvement.

Transcept Pharmaceutical, Inc. has provided a comprehensive development program for Intermezzo that exceeds previous applications in the same drug class. The results of the

well-designed driving trial are a very welcome addition to the knowledge base on the insomnia medications. However, at this stage, I would not recommend approval for Transcept at the 3.5 mg dose strength. More information is needed about next-morning functioning, as well as the possible relationship to plasma concentration levels for all the hypnotic medications before better benefit/risk generalizations can be made. Additional scrutiny is placed on Intermezzo since it is targeted for a new indication of middle-of-the-night dosing which highlights these concerns.

2. Introduction

NDA 22-328 was submitted by Transcept Pharmaceuticals Inc. on 9/30/2008. Intermezzo (zolpidem tartrate sublingual tablet) is proposed for the treatment of insomnia characterized by middle-of-the-night (MOTN) awakenings with difficulty returning to sleep. Zolpidem tartrate is currently marketed as a non-benzodiazepine of the imidazopyridine class for the treatment of insomnia, and this application is submitted under section 505(b)(2) of the FD&C Act with Ambien (zolpidem tartrate 10 mg and 5 mg, approved 12/16/1992, as the Reference Listed Drug (RLD). Ambien® has an indication for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

Due to the time of dosing, the doses for Intermezzo are lower, 3.5 mg (for adults), and 1.75 mg (for the elderly or patients with hepatic impairment). This would be the first insomnia drug to be marketed for the indication of middle-of-the-night insomnia. Intermezzo should not be taken if less than 4 hours of bedtime remains.

At the conclusion of the original review cycle, the reviewers concluded that concerns remained about safety of the middle-of-the-night use, and whether the medication might pose any early-morning safety risk, particularly if used with less than the recommended four hours of remaining sleep time.

Transcept Pharm. proposed packaging Intermezzo (b) (4) Since the medication would probably be kept at bedside, there is potentially a chance of inadvertently repeating the dose on a subsequent awakening.

PK data was evaluated only in a few early studies. There appears to wide variability in the PK values obtained, even in young, healthy male and female subjects. In addition, there is evidence that female subjects often had considerably higher plasma levels than the males. These pharmacokinetic factors are not unique to Intermezzo, and have been noted in the reference drug Ambien®, and other sleep-aid medications.

It was also felt that the PD measurements chosen may not be sufficiently sensitive to evaluate morning residual effects (especially for sustained attention or reflexes/coordination psychomotor skills). Subject self-assessment of alertness/sleepiness may not be reliable due to residual drug effects of which the subjects are unaware.

Transcept was notified October 28, 2009 that the review cycle for Intermezzo concluded that there was evidence of efficacy, but additional demonstration that Intermezzo can reliably be used safely would be required to support approval. The following issues were cited as the key deficiencies that needed to be addressed:

- Continuing concerns over possible middle-of-the-night medication errors that had been discussed in earlier teleconferences with the Division (Minutes of telecons 4/22/09 and 7/24/09);
    - Inadvertent dosing with less than 4 hours of bedtime remaining
    - Inadvertent re-dosing in a single night
- Lack of evidence that even when used as directed, Intermezzo is adequately free of next-day adverse effects on driving (i.e. assurance that blood/tissue concentrations after final awakening do not result in residual effects).

The Sponsor has addressed the concerns of the Division in the Complete Response resubmission dated January 14, 2011. Included are the re-packaging of Intermezzo in individual-use packets so that a single tablet can be left at bedside, revised use instructions along with a dose-timing wheel, and the results of Study ZI-18, a next-morning highway driving assessment.

On April 26, 2011, the division requested additional data for sub-group analyses regarding pharmacokinetic (PK) and pharmacodynamic (PD) data from the trials. The Sponsor was asked to cull results from all the trials that collected either PK or PD information, or both, during the Intermezzo development program. The Sponsor responded with a May 26, 2011 submission of analyses of PK and PD data from 3 trials each that included PK data, PK/PD data, and PK data.

3. Background

3.1 Summary of Regulatory Activity Related to Submission

September 30, 2008 - Transcept submitted a new drug application (NDA) for Intermezzo (zolpidem tartrate) sublingual tablet 1.75 mg and 3.5 mg under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with Ambien® 5m and 10 mg as the reference drug.

April 22, 2009 – in a teleconference the Division expressed concerns about potential medication errors that might occur with the unique MOTN dosing regime. These included possible inadvertent dosing with less than 4 hours of bedtime remaining, or amnesia-related inadvertent re-dosing in a single night. The sponsor was requested to provide a proposed plan to address the possible risks. Additional information was requested regarding effects if the drug was taken with less than 4 hours bedtime remaining, and evaluation, if there is any data, on when patients actually woke up. A possible use study was suggested by the Division.

May 29, 2009 – Transcept submitted a major amendment related to the Risk

Evaluation and Mitigation Strategy (REMS) [redacted]

Regarding the amnestic properties of zolpidem, a 1997 study was cited that a low dose of zolpidem in Intermezzo would not cause memory impairment (Mintzer et al, Behavioural Pharmacology, 1997). Also, asserted was that patients with insomnia are hyper-aroused, and therefore less vulnerable to sleepiness-related impairments in memory. The sponsor proposed a revised Medication Guide [redacted]

June 26, 2009 - The goal date was extended by three months, to October 30, 2009, to provide time for a full review of the submission.

July 24, 2009 - telecon, the Division indicated that it is not clear from the Medication Guide how the instructions to patients could prevent inadvertent double dosing in the middle of the night, and asked Transcept to submit a proposal on how to further clarify instructions for patients in order to minimize the risk of taking a second dose.

July 30, 2009 - amendment submitted by Transcept for follow-up concerning potential medication errors. [redacted]

September 17, 2009 – Transcept response to Carton/Carton Labeling Comments Changes implemented, as per Agency comments, included artwork & color schemes revised to improve the differentiation between the two dose strengths, incorporation of all specific language revisions suggested by the Agency, revision of layout and formatting of key statement to increase their prominence, and instructions on how to close the [redacted] unit.

October 28, 2009 – Complete Response letter issued by the Division. The letter acknowledged that there was substantial evidence of effectiveness of Intermezzo for the indication. However, approval of the application would require assurance that blood/tissue concentrations after final awakening do not result in residual effects. The Agency requested data regarding the next-morning driving performance following MOTN use of Intermezzo. Also, additional reassurance was required regarding potential medication dosing errors.

January 20, 2010 – End of Review Meeting Minutes. The Division felt the individual-dose packaging proposed by the sponsor in their resubmission would decrease concerns about the risk of inadvertent re-dosing, however concern remained bout the risk of impaired driving resulting from other dosing errors. Possible designs for a driving study were discussed.

March 15 & 19, 2010 – CMC reviewed the Sponsor's revised proposal individual drug product packaging, and recommended a demonstration run of the 3.5 mg tablets at 1/10th of the commercial batch size.

March 24, 2010 – Telecon the Agency agreed to the proposed driving study.

October 8, 2010 – Submission of the Statistical Methods and Interim Analysis Plans

January 14, 2011 – Resubmission/Class 2 response submitted by Transcept.

February 23, 2011 – email to the sponsor requesting additional information. Requested was the submission or location of the original electronic source files for the SDLP endpoint prior to removal of "data artifacts", and analysis dataset(s) for the comparative analysis of data in the literature compared to the ZI-18 driving study, along with define file(s) and relevant programming code used in the analysis.

February 28, 2011 – informal telecom to discuss statistical analysis of Study ZI-18 Dr. Vuurman participated to describe the methodology of the study and the statistical procedures. The Division voiced concerns that elimination of 'artifact' data, without having pre-specified the rules for data editing in the protocol or statistical analysis plan, may bias the results. More documentation was requested, specifically:

1. the SOPs and coding conventions for collecting, editing, and analyzing the Driving study data,
2. a graphic display of video data mapping out what data was eliminated, and
3. Ascii files (raw data, i.e., before removal of "artifacts") in SAS transport format.

The sponsor agreed to send this information in as soon as possible.

March 11, 2011 – email to the sponsor with follow-up questions related to the video images received from Dr. Vuurman's files. These included additional information on artifacts, slow speed episodes, interactions between the instructor and driver, reflection events, and whether lateral position tracing could be converted to 'distance from lane line'.

March 29, 2011 – PLR edits for labeling were sent to the sponsor.

May 4, 2011 – telecom, the Division elaborated on the request for additional PK and PD data from all the trials in which any assessments of either or both PK and PD evaluations were done.

April 18 & 26, 2011 – emails sent to the sponsor (transcripts of the May 4th telecom) regarding the request for additional information on the relationship of individual patient response related to demographic or other factors. Analysis of PK and/or PD data from all trials (regardless or dose or formulation) was requested. Interest was expressed regarding how factors known to affect PK, such as age and fed/fasted state might interact with other

baseline factors (such as gender). Recommendations were made for graphic representation of the data.

May 26, 2011 – Transcept submitted the additional data requested, and included a summary report prepared by (b) (4) concerning the effect of demographic factors on individual patient response to Intermezzo.
The submission includes the following:

- Summary Report Part 1: Analysis of PK and PD data from new drug application studies of Intermezzo
  - Appendix A: Summary of demographic and kinetic variables
- Summary Report Part 2: Analysis of next-day residual effects in clinical and driving studies after middle-of-the-night dosing with Intermezzo
  - Appendix B: Regression analysis for clinical and driving studies
- Appendix C: Summary of PK/PD analyses
  - Section 1: Summary tables for PK parameters by sex, body weight, BMI, age, and race
  - Section 2: Summary tables for PD parameters by sex, body weight, BMI, age, and race
  - Section 3: Box plots of PK and PD variables vs. demographic parameters (item #2 in e-mail of 26 April 2011)
  - Section 4: Grouped PK and PD plots over time, by demographic parameter (item #3 in e-mail of 26 April 2011)
  - Section 5: Scatter plots of PK parameters vs. demographic factors
- Appendix D: Graphs showing individual subject data over time
- Descriptions of the analyses for Appendix C and D

3.2 Drug Development Background

Currently, marketed hypnotics are approved only for bedtime use. Since insomnia may be sporadic, use of the medication may be prophylactic without filling a need on the nights when insomnia might not have occurred. Intermezzo was designed as a low-dose (3.5 mg and 1.75 mg) sublingual zolpidem to be used only when MOTN insomnia actually occurs. Dosing should occur only once during a night, and should be used, as needed (PRN), only if at least 4 hours of bedtime remain before morning activities. The Intermezzo doses are lower than the approved reference drug (Ambien® 10 mg and 5 mg). PK data showed a plasma concentration of 20 ng/mL within 20 minutes, and C_{max} of 64 ng/mL and 32 ng/mL for the 3.5 mg and 1.75 mg doses, respectively. T_{max} and $t_{1/2}$ remained stable over the doses, with a T_{max} of ~ 36 minutes, and a $t_{1/2}$ of ~ 2 ½ hours (similar to Ambien). The results, by LS mean ratios, show a consistent dose-proportionality for the 3.5mg and 1.75 mg dose strengths, but not a 1.0 dose. Mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher in elderly subjects compared to Adults.

The Intermezzo development trials (all phases) included a total of 618 subjects with at least one exposure to Intermezzo. The original NDA application included the two pivotal (Phase 3) trials examining the effectiveness and safety of Intermezzo for MOTN

insomnia. Also included were several clinical pharmacology studies, the requisite chemistry and manufacturing controls (CMC) information, and other data.

Description of Pivotal (Phase 3) Trials:

- ZI-06-010: an in-clinic, multi-center, placebo-controlled, polysomnography (PSG)-monitored cross-over trial of two zolpidem SL dose strengths (3.5 mg and 1.75 mg) in 82 non-elderly adult subjects (71% female) with MOTN insomnia. Duration of active treatment was three 2-night periods with wash-out periods between. Subjects were awakened after 4 hours of sleep, and required to stay awake for 30 minutes post-dosing.

  The trial met its primary Latency to Persistent Sleep ($LPS_{MOTN)}$ endpoint for the zolpidem SL 3.5 mg dose, and also for the 1.75 mg dose by decrease of ~18 min. and ~11 min. respectively compared to placebo. The secondary endpoint of total sleep time (TST_{MOTN}) increased significantly for both zolpidem groups compared to placebo. Neither zolpidem SL 3.5 mg or 1.75 mg doses showed a significant decrease on awake time after initial post-dosing sleep onset (WASO) or number of awakenings (NAW), both of which the sponsor had designated as exploratory endpoints. The subjective reports on the Morning Sleep Questionnaire paralleled the PSG findings. Tests of alertness, and the Digit Symbol Substitution Test (DSST) were administered in the morning in Study ZI-06-010, and neither dose was different from placebo.

- ZI-12: An outpatient (at-home), parallel-group trial in 294 non-elderly adult subjects (68% female) with MOTN insomnia. The trial used only the Intermezzo 3.5 mg dose strength. Subjects were randomized 1:1 to 3.5 mg zolpidem SL or placebo. Duration of active treatment was 4 weeks (28 nights) of "as needed" self-administered dosing after gaining approval via Interactive Voice Recording System (IVRS) (note: permission refused if <4 hours of bedtime remaining). A Morning Sleep Questionnaire was evaluated for analysis of endpoints.

  There was a treatment-attributable decrease in the primary endpoint subjective Latency to Sleep Onset ($sLSO_{MOTN}$) of ~ 17 minutes for the zolpidem SL group compared to the placebo group. The first secondary endpoint (of the hierarchy) was subjective Total Sleep Time following middle-of-the-night-awakening ($sTST_{MOTN}$) which was directionally positive (mainly in the first week), but not statistically significant. The zolpidem tartrate SL 3.5 mg showed significant effects on subjective Number of Awakenings ($sNAW_{MOTN}$) and subjective Awake Time After Sleep Onset ($sWASO_{MOTN}$) on the 4-week treatment average, and on Weeks 1,2 and 3 (not Week 4). An exploratory questionnaire endpoint of improvement in sleep quality on nights study medication was taken showed significant difference favoring the zolpidem group for the 4-week mean, and each of the weeks. Sleepiness, and alertness, on the mornings following study drug use, was measured on a 9-point scale on a subjective questionnaire, and the difference favored Intermezzo over placebo.

Overall both trials could be considered to have adequately demonstrated efficacy for zolpidem SL 3.5 mg. The 1.75 mg dose strength also appears to have demonstrated efficacy, although not consistently at a statistically significant level.

The safety review was based on pooled data from 8 trials. A total of 436 subjects received at least one dose of zolpidem SL 3.5 mg, 130 subjects received 1.0 mg/1.75 mg, and 315 subjects received placebo. The only serious AEs did not involve subjects on active drug treatment, and withdrawals/discontinuations were generally not drug-related. In the pooled safety data, the most frequently reported AEs were somnolence and fatigue, as expected in with a sedative-hypnotic drug, especially in the daytime trials. Headache was reported by 5.5% of subjects receiving zolpidem 3.5 mg, and by 3.1% of subjects in the 1.0/1.75 mg dose strength groups. Review of data relating to the sublingual administration of the drug raised no concerns.

At the end of the review cycle, the Division sent a Complete Response Letter to Transcept stating that additional evaluation would be needed on the following issues:

- Inadvertent re-dosing in a single night
- Inadvertent dosing with less than 4 hours of bedtime remaining
- Possible next-day adverse effects on driving
- Possible relationship between PK profile and pharmacodynamic differences
- Possible relationship between demographic variables and pharmacodynamic differences

4. Review of Complete Response (CR) Issues

Revised packaging with relevant instructions and labeling, was submitted sequentially. The driving trial results for Protocol ZI-18 were submitted February 14, 2011. The sponsor submitted a PK and PK/PD amendment to the CR on May 26, 2011.

4.1 Inadvertent re-dosing in a single night

In the home-use pivotal trial, ZI-12, monitoring of pills used, compared to the voice system records, indicated that more tablets were used than could be accounted for, which suggested that there may be a possibility of inadvertent re-dosing . The sponsor initially (b) (4)

Concerns remained that due to the unique middle-of-the-night use, (b) (4)

Recommendation was made by the Agency that a carton containing individual blisters would be preferable. The carton could be kept with other medications, and a single dose left at bedside each night. If a tablet is used, then on a subsequent awakening, there

would be the evidence of an individual empty blister package to remind the patient. The sponsor agreed with the recommendation, and samples of the individual packaging were submitted for review, and deemed acceptable by all the reviewers.

4.2 Inadvertent dosing with less than 4 hours of bedtime remaining.

In discussions regarding the possibility of dosing too close to morning activities, an in-use study, to be conducted pre-approval, was considered, but felt to be unlikely to provide a meaningful demonstration of the potential for dosing errors. As in the outpatient pivotal trial, the study design would be likely to influence patterns of use. To address the possible risk of dosing too late in the night, the Sponsor has proposed a 4-element packaging system including a unit-dose pouch, Patient Instructions for Use (PIU), a dose timing chart, and a timing-wheel to aid in preventing use of the medication with less than 4 hours of remaining bedtime. A 4-month study including 74 insomnia participants in four states evaluated the 4-element packaging system on a 7-point scale. The labeling comprehension study concluded that patients will be able to understand and correctly use the 4-element packaging system. However, it was noted that only 8% of all respondents completed high school or less. The proposed changes were reviewed by Loretta Holmes, Division of Medication Error Prevention and Analysis (DMEPA), on April 15, 2011; see full review. If the medication is used as recommended, these measures should prevent the risk of dosing too close to morning activities, but as with other sleep-aid products, it would be difficult to impossible to prevent purposefully dosing too late.

4.3 Possible next-day adverse effects on driving – review of ZI-18

The Division was concerned that next-day subjective self-assessment of alertness/sleepiness may not be reliable following the use of a hypnotic medication. The early morning assessments conducted in previous insomnia medication trials, such as the Digit Symbol Substitution Test (DSST), the Choice Reaction Time (CRT) and Visual Analogue Scale (VAS) do not evaluate aspects such as sustained attention, reflexes, and diversified decision-making. At the recommendation of the Division, Transcept conducted a highway driving study (Protocol ZI-18) which was submitted to the Division February 14, 2011 for review.

The early-morning highway driving trial (ZI-18) follows middle-of-the-night zolpidem tartrate SL 3.5 mg dosing to evaluate driving ability at 3 hours (ZST 3h) or 4 hours (ZST 4h) after use, compared to placebo, or bedtime zolpiclone (ZOP) use at 9 hours post-dosing (Table 1).

Table 1. Protocol ZI-18 – Next-day driving trials.

Type of Study	Study Identifier	Study Objective	Study Design & Type of Control	Study Drug Dosage & Timing	Subjects	Duration of Treatment
PD	ZI-18	Assessment of next-morning driving performance after middle of-the-night dosing	Double-blind, randomized, placebo-controlled, four-way crossover (4 single nights)	Zolpidem tartrate SL 3.5 mg: 4 hr. pre-driving Zolpidem tartrate SL, 3.5 mg: 3 hr. pre-driving Placebo Zolpiclone 7.5 mg: 9 hr. pre-driving	40 healthy subjects (21-64 years old)	4 single nights of treatment over a maximum of 6 weeks

PD= pharmacodynamic

Title of Study: Assessment of Next-Morning Driving Performance after Middle of the Night Administration of Zolpidem Tartrate Sublingual Tablet 3.5 Mg in Healthy Adult Volunteers: Single-Center, Double-Blind, Randomized, Placebo-Controlled, Four-Way Crossover Study.

Principal Investigator: Annemiek Vermeeren, Ph.D. (Maastricht University, Maastricht, The Netherlands)

Trial Design:
The driving trial was designed as a single-center, double-blind, randomized, placebo-controlled, four-way crossover study, with 40 adult healthy male and female subjects (ages 21-64 years, and driving $\geq$ 3,000 km/yr) randomized to receive 4 treatments in one of 24 possible treatment sequences over 4 treatment periods:

- zolpidem tartrate SL tablet 3.5 mg - 4 hours before driving test (ZST 4h),
- zolpidem tartrate SL tablet 3.5 mg - 3 hours before driving test (ZST 3h),
- zopiclone oral capsule 7.5 mg - 9 hours before driving test (ZOP),
- placebo – matching (capsule or SL tablet)

Zopiclone 7.5 mg tablet (Imovane®) enclosed in a capsule for oral use was included in the protocol to serve as positive control/assay sensitivity. In previous studies, zopiclone demonstrated significant differences in highway driving when compared to placebo (Leufkens, et al., 2009; Menzin, et al., 2001. In the United States, zopiclone is not commercially available, although its active stereoisomer, eszopiclone, is sold under the name Lunesta. The eszopiclone/zopiclone difference is in the dosage—the strongest eszopiclone derivative dosage contains 3 mg of the therapeutic stereoisomer, whereas, the highest zopiclone dosage (7.5 mg) contains 3.75 mg of the active stereoisomer. Placebo study drug was presented as either a capsule matching zopiclone, or a sublingual tablet matching zolpidem.

Within the screening phase, subjects spent one night in the study unit to practice one drive in the dual-controls test car with the instructor, and one dose of placebo was given to demonstrate sublingual dosing. For the testing period, subjects were admitted to the sleep unit at ~ 22:00h. Alcohol or caffeine-containing products were not to be consumed for >6 hours prior to check-in. Routine activities were done (drug testing, concomitant meds and vital signs checks, and study drug (either placebo or zopiclone capsule) administered at bedtime (~23:15h). Subjects were awakened at 04:15 or 05:15 if scheduled for driving test 4 hours or 3 hours, respectively, post-MOTN dosing and received either zolpidem SL 3.5 mg or placebo tablets, and allowed to resume sleeping until rise time at 07:30h (Table 2). Preceding the Highway Driving Test (at ~08:15h), subjects were allowed time for toileting, dressing, AE questioning, and a light breakfast (no caffeine). Due to multiple driving evaluations in a day, start times for subjects were staggered by 5-10 minutes. Subjects were driven home and cautioned to avoid driving unaccompanied for >24 hours after the last dosing. Treatment periods were separated by at least 3 days. An end-of-study visit for labs was conducted within 10 days. (See Schedule of Assessments, Appendix Table 1).

Notable in the ZI-18 trial is the timing of the driving. Subjects were awakened at either 2¼ or 3¼ hours after the MOTN dosing so that the driving trials could commence at 3 hours and 4 hours post-dosing, respectively. Previous driving trials conducted for insomnia medications were timed with the assumption that subjects would not be driving for >1 hour after awakening from the recommended amount of bedtime.

Table 2. Driving trial awakening and driving commencement times – ZI-18.

Treatment condition:	**Bedtime dose**		**MOTN dose**		**Rise time**	**Test**
A1	23:15h	ZOP	05:15h	Placebo	07:30h	08:15h
A2	23:15h	ZOP	04:15h	Placebo	07:30h	08:15h
B 3h	23:15h	Placebo	05:15h	ZST	07:30h	08:15h
C 4h	23:15h	Placebo	04:15h	ZST	07:30h	08:15h
D1	23:15h	Placebo	05:15h	Placebo	07:30h	08:15h
D2	23:15h	Placebo	04:15h	Placebo	07:30h	08:15h

Source: Study Report, Study ZI-18, p. 36

The driving test was performed on a designated highway circuit of ~100 km with an instructor, and a car equipped with dual controls and validated instruments (including infrared roof-top mounted camera) to record lateral position variance and speed. The lateral position of the car relative to the left lane boundary and the car's speed are continuously recorded and digitally sampled at 4Hz. Subjects were instructed to maintain a constant speed (95 km/hr) and a steady position within the right lane of traffic (except for passing vehicles as needed). Excluded from the collected data are the periods spent in lane changes due to overtaking vehicles, or those caused by other road or traffic conditions.

The Standard Deviation of Lateral Position (SDLP) has previously been used as an assessment of driver control in several trials (Vermeeren et al., 2002; 1998; 1995; O'Hanlon

et al., 1995; O'Hanlon and Ramaekers, 1995). Driving impairment is evaluated by identification of subjects whose SDLP exceeded a pre-specified threshold value. Visual representation of the SDLP is shown in Fig. 1. Past studies have recorded the placebo group SDLP at generally between 18 and 22 cm. Increased SDLP suggests increased weaving with repeated out-of-lane excursions into the road shoulder and adjacent lane of traffic. When trying to evaluate SDLP increments (with treatment SDLP minus placebo SDLP) to corresponding Blood Alcohol Concentration (BAC) levels, the estimated relationship previously used was: +2.6 cm (BAC 0.05%),+ 4.1 cm (BAC 0.08%), and +5.3 cm (BAC 0.10%) (Verster, 2004).

Source: Verster et al. (2004) 8, 309–325

Objectives:
Primary:

- To assess the risk of impaired driving in the morning at 3 and 4 hours after a middle-of-the-night dose of zolpidem tartrate sublingual tablet 3.5 mg.

Secondary:

- To assess aspects of driving performance as they relate to absolute standard deviation of lateral position (SDLP), and standard deviation of speed (SDS).

Primary Endpoint: Impaired Driving Performance (ImpDr)
Impaired Driving Performance (ImpDr) is defined by the formula below:

Impaired Driving Performance (ImpDr) is a binary indicator defined for subject i to be

1 – if Treatment SDLP[i] – Placebo SDLP[i] > 2.5 cm, or if the test was prematurely terminated due to impaired driving performance
0 - otherwise

For the primary endpoint, the SDLP threshold value is set at t*=2.5 cm for the group driving 4 hours after zolpidem 3.5 mg dosing.

Secondary Endpoints:

- Impaired Driving Performance (ImpDr) with threshold values (t*) of 2.0 and 3.5:
  1 – if Treatment SDLP[i] – PlaceboSDLP[i] > t* cm, or if the test was prematurely terminated due to impaired driving performance
  0 - otherwise

- SDLP in centimeters in the driving test.

- Mean standard deviation in speed (SDS).

For the secondary endpoints, the SDLP threshold value is set at 2.0 cm, and 3.5 cm as defining "impaired" driving for all the groups. The entire range of SDLP was also evaluated and compared for each group, as well as the effects of timing and group order. The mean standard deviation in speed (SDS) was also a secondary endpoint.

Exploratory Analyses:
Symmetry Analyses of Impaired Driving Performance similar to the primary and secondary endpoints evaluating threshold values from 1.75 cm to 6.5 cm by increments of 0.25 cm.

Disposition of Subjects:
A total of 44 subjects were screened; 40 subjects were randomized (20 males, 20 females, median age 32 years (range 21-64 years for males, 22-60 years for females). Included were 6 males and 2 females of age >55 years. Race/ethnicity - 39 subjects white, 1 'other' – not black or Asian. All 40 subjects received study drug in all 4 periods, and were included in the 160 driving tests (40 tests per period). If the driving trial was terminated early due to sedation of the driver, the SDLP and SDS values obtained prior to termination were used. There were no premature withdrawals; all were considered to have completed the trial. The only protocol deviation reported was the randomization schedule resulting in A and C groups of 19 and 21 rather than 20 per group.

Efficacy Results

Table 3 summarizes the SDLP results of the driving trial. Overall, the data indicate that driving was least impaired when subjects were in the placebo arm, and increasing mean SDLP was evidenced in zolpidem 4 hours (ZST 4h), zolpidem 3 hours (ZST 3h), and zopiclone 9 hours (ZOP) by significant intervals.

Of interest is the mean for each treatment arm which indicates that despite significant p-values, the mean differences are quite small. Subtracting the placebo result, the LS Mean for ZST 4h is 0.8 cm, ZST 3h is 1.5 cm, and for ZOP 9h is 2.5 cm (which puts the zopiclone difference at the threshold for the definition of SDLP driving "impairment"). The mean difference in SDLP for ZST 4h and ZST 3h compared to placebo does not reach the t*=2.5 cm threshold of change. Statistical analysis by treatment, and period (driving period 1, 2, 3 or 4) showed significance, but analysis by sequence (order of study drugs) did not.

Table 3. Summary of Standard Deviation of Lateral Position

	Placebo (N=40)	**ZST 4h (N=40)**	**ZST 3h (N=40)**	**ZOP (N=40)**	
SDLP (cm)					
Mean (SD)	15.9 (3.14)	16.7 (3.34)	17.3 (3.57)	18.3 (4.01)	
Median	16.4	16.7	17.2	18.0	
Min, Max	8.7, 22.2	9.2, 26.2	9.1, 26.2	8.8, 26.8	
ANOVA Analysis					
LS Mean (SE) treatment	15.9 (0.60)	16.7 (0.60)	17.3 (0.60)	18.3 (0.60)	
LS Mean (SE) difference from placebo[1]		0.8 (0.34)	1.5 (0.34)	2.5 (0.34)	
95% CI of LS difference from placebo[1]		0.1, 1.5	0.8, 2.1	1.8, 3.1	
P-value[2] (df) treatment group difference		0.0174 (114)	<0.0001 (114)	<0.0001 (114)	
Treatment					<0.0001 (3, 114)
Period					0.0171 (3, 114)
Sequence					0.6352 (23, 16)

Note: analysis is based on reported data as available for all subjects

1 LS Mean difference from Placebo is Treatment Group (ZST 3h, ZST 4h, ZOP) – Placebo

2 P-value is based on ANOVA model with fixed effects for sequence, period and treatment (Placebo, ZST 4h, ZST 3h, and ZOP), a random effect for subject within sequence, and assuming compound symmetry covariance structure; the p-values are reported from LS Mean difference between Treatment Group (ZST 4h, ZST 3h and ZOP) and Placebo

Source: Study Report, Study ZI-18, based on Table 14.2.2-2, p. 67

Table 4 was submitted by the sponsor to present the results of the symmetry analysis of ZST 4h versus placebo. The table relates each threshold level to a p-value. Similar tables of symmetry analysis are included for the ZST 3h and ZOP data in Appendix Tables 2 &3.

Based on the symmetry analysis, the Sponsor concludes that there were no statistically significant treatment effects at any threshold.

Table 4. Levels of Threshold in Relation to Impaired Driving Performance and P-values (ZST 4h)

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZST 4h	1.75	8	29	3	0.200	0.075	2.27	0.2266
	2	6	33	1	0.150	0.025	3.57	0.1250
	2.25	5	34	1	0.125	0.025	2.67	0.2188
	2.5	5	34	1	0.125	0.025	2.67	0.2188
	2.75	4	36	0	0.100	<.001	4.00	0.1250
	3	3	37	0	0.075	<.001	3.00	0.2500
	3.25	2	38	0	0.050	<.001	2.00	0.5000
	3.5	2	38	0	0.050	<.001	2.00	0.5000
	3.75	2	38	0	0.050	<.001	2.00	0.5000
	4	1	39	0	0.025	<.001	1.00	1.0000
	4.25	1	39	0	0.025	<.001	1.00	1.0000
	4.5	1	39	0	0.025	<.001	1.00	1.0000
	4.75	1	39	0	0.025	<.001	1.00	1.0000
	5	1	39	0	0.025	<.001	1.00	1.0000
	5.25	1	39	0	0.025	<.001	1.00	1.0000
	5.5	1	39	0	0.025	<.001	1.00	1.0000
	5.75	1	39	0	0.025	<.001	1.00	1.0000
	6	1	39	0	0.025	<.001	1.00	1.0000
	6.25	1	39	0	0.025	<.001	1.00	1.0000
	6.5	0	40	0	<.001	<.001		

Source: Study Report, Study ZI-18, based on Table 14.2.1-2

P-values assessments are included by the sponsor, however in this type of trial with small number of subjects, and small differences in measurement, p-values do not provide much clarification, or have much meaning of clinical significance.

Primary Endpoint:
Impaired Driving Performance (ImpDr) at DSDLP t 2.5 cm for ZST 4 h*

For the primary endpoint, the SDLP threshold value is set at t*=2.5 cm for the group driving 4 hours after zolpidem 3.5 mg dosing.
Evaluation of the primary endpoint by symmetry analysis did not provide adequate information. For this review, the SDLP scores for ZST 4h were re-analyzed in relation to the SDLP scores for placebo driving in Appendix Table . The results are presented in Table 5 which summarizes the SDLP results (SDLP treatment drug minus SDLP placebo) by level of threshold (t*). The Transcept protocol set the additional thresholds for evaluation at t*=2.0 cm and t*= 3.5 cm, which are evaluated as secondary endpoints. For the purpose of this review, I have added thresholds at 5.0 cm, and 6.5 cm.

The protocol specified the primary outcome measure to be conducted at t* = 2.5. At the threshold of t*=2.5 cm, 5 subjects (12.5%) were designated "impaired", and 1 (2.5%) "improved".

Table 5. Summary of "Impaired" Driving performance by SDLP Threshold

SDLP threshold (cm)	ZST 4h (N=40)	ZST 3h (N=40)	ZOP 9h (N=40)
t* = 2.0			
Impaired	6 (15.0%)	13 (32.5%)	19 (47.5%)
Improved	1 (2.5%)	2 (5.0%)	0
Neutral	33 (82.5%)	25 (62.5%)	21 (52.5%)
p-value	0.1250	0.0074	<0.0001
t* = 2.5			
Impaired	5 (12.5%)	10 (25.0%)	18 (45.0%)
Improved	1 (2.5%)	1 (2.5%)	0
Neutral	34 (85.0%)	29 (72.5%)	22 (55.0%)
p-value	0.2188	0.0117	<0.0001
t* = 3.5			
Impaired	2 (5.0%)	7 (17.5%)	14 (35.0%)
Improved	0	33 (82.5%)	0
Neutral	38 (95.0%)	0	26 (65.0%)
p-value	0.5000	0.0156	0.0001
t* = 5.0			
Impaired	1 (2.5%)	2 (5.0%)	9 (22.5%)
Improved	0	38 (95.0%)	0
Neutral	39 (97.5%)	0	31 (77.5%)
t* = 6.5			
Impaired	1 (2.5%)	1 (2.5%)	4 (10.0%)
Improved	0	0	0
Neutral	40 (100%)	39 (97.5%)	36 (90.0%)

t* = SDLP threshold
Clin. Review chart

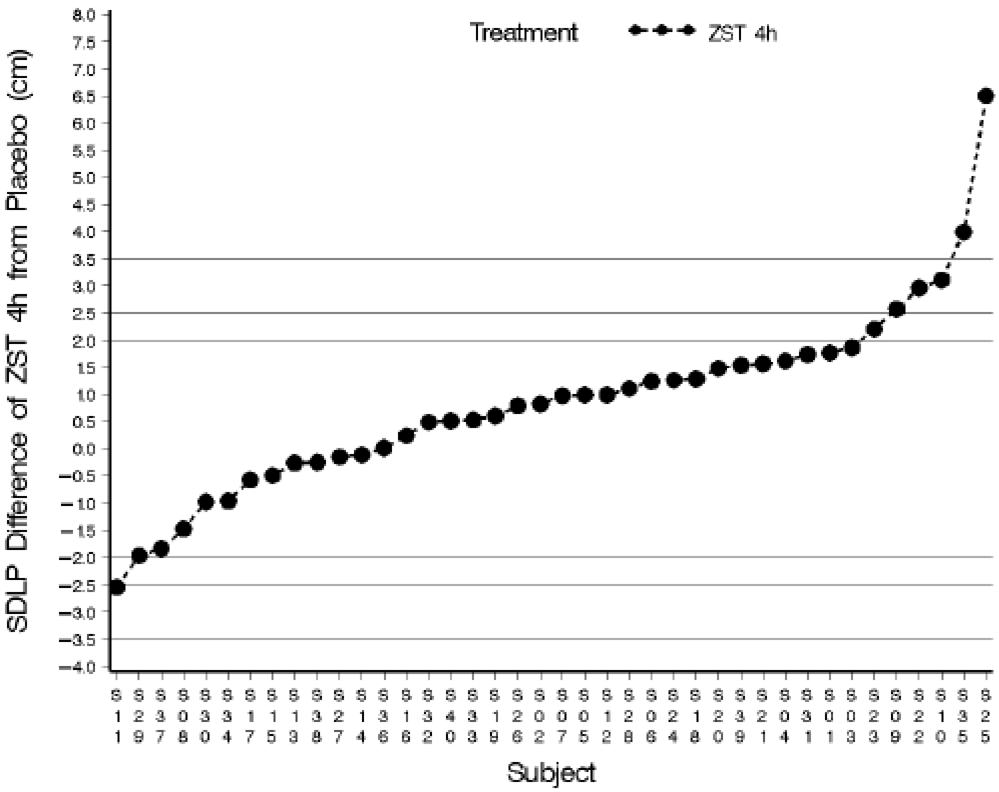
Note: Over-encapsulation of the zopiclone capsule was done in this trial. It is possible that might have affected the PK parameters for the medication, possibly extending the T½ and early morning effects, although testing was conducted at 9 hours post-dosing, rather than 8 hours.

In the ZST 4h group, at SDLP t*=2.5 cm, the primary endpoint of the trial, the "improved "driver (male, 43 yrs) had a recorded decline in SDLP of 2.54 cm, compared to driving in the placebo group. The drivers designed "impaired drivers" included 2 females, both 23 yrs, and 3 males, ages 41, 36, and 23 yrs, the latter two were also designated "impaired"

at the sponsor-designated t*=3.5 cm SDLP threshold (at 3.99 cm and 6.50 cm, respectively).

Fig. 2 illustrates the SDLP differences (for ZST 4h-placebo) by individual subjects allowing a visual representation of the size differences ranked by smallest to largest. Lines for the designated threshold are indicated on the plot. None of the driving tests for zolpidem 3.5 mg at 4 hours post-dosing were terminated early.

Fig. 2. Plot of SDLP differences (ZST 4h-Placebo) for individual subjects



Source: Study Report, Study ZI-18, p. 55.

There is considerable variability/"noise" within the driving trials. The mean SDLP pattern summarized in Table 5 above (of placebo<ZST 4h <ZST 3h <ZOP) actually occurs for only 8 of the 40 subjects (20%). ZOP, the predicted "worse case" sensitivity indicator, had the largest mean SDLP for only 22/40 (55%) of the subjects for 4 hour post-dosing driving.

Secondary Endpoints:

SDLP Δ in centimeters in the driving test

Values of SDLP t* ranging from 1.75 to 6.5 at 0.25 cm increments were listed. The ZI-18 submission does not furnish much discussion on the secondary or exploratory endpoints for the SDLP except to state that for ZST 3h group, statistically significant asymmetries were found at threshold values from 1.75 to 4.0 cm. signifying that "more subjects beginning a drive 3 hours after taking ZST experienced a decrement (increase in

SDLP exceeding the specified positive threshold) rather than an improvement (decrease in SDLP below the specified negative threshold) in their driving performance".

In this review, the symmetry analyses were not felt to be helpful or informative for the driving evaluations. Focus instead was placed on the driving results for the individual drivers for comparison by treatment arms, and

Impaired Driving Performance (ImpDr) with threshold values (t) of 2.0 and 3.5*
Secondary outcome measures set the value of SDLP change at the sponsor-designated thresholds of t* = 2.0 cm and t* = 3.5 cm for evaluation. Except for the presentation in tables, no discussion of the secondary results was presented.

For the 4 hour post-dosing results using the expanded thresholds: the t* = 3.5 cm threshold, as discussed above, has 2 designated "impaired" drivers (5%), with one of those being "impaired" at the t* = 6.5 cm level. The 2.0 cm threshold is not of much interest or concern in comparison to the higher SDLD thresholds, and was included by the sponsor probably for the opportunity of possibly including "improved" driver results (1 was noted, 2.5%, compared to 6 "impaired", 15%).

Looking specifically at the "impaired" driving performance (ImpDr) for zolpidem at 3 hours post-dosing (ZST 3h), at the SDLP t* =2.5 cm, 10 subjects (25.0%) were designated "impaired", and 1 (2.5%) "improved". At the SDLP t* = 2.0 cm threshold, 13 subjects (32.5%) were "impaired" and 2 (5.0%) "improved". At the SDLP t* =3.5 cm threshold, there were 7 subjects (17.5%) "impaired", and none "improved". Two subjects (5%) remained at the SDLP t*=5.0 cm, and one (2.5%) at the SDLP t*=6.5cm.

As previously discussed, next-day driving after treatment with zopiclone has been demonstrated in previous clinical trials. Zopiclone 7.5 mg, tested with driving commencing 9 hours post-dosing, was included in Protocol ZI-18 as an indicator of sensitivity. At the SDLP threshold of $\geq$2.5 cm, 18 subjects (45.0%) were designated "impaired" and none "improved". At the 2.0 cm SDLP threshold, 19 (47.5%) were "impaired", and at the 3.5 cm threshold, 14 (35.0%) "impaired". None of the subjects were designated "improved" at any threshold. Even if using a t*=5 cm threshold, 9 subjects (22.5%) were designated "impaired", including 4 (10.0%) at the 6.5 cm threshold.

Mean standard deviation in speed (SDS)
Table 6 summarizes the Standard Deviation of Speed (SDS). Of interest is the inconsistency between treatment arms. The LS Mean difference from placebo was smallest for zolpidem 3 hours (ZST 3h), and nearly identical for ZST 4h and zopliclone (ZOP). Again, statistical difference was indicated for treatment and period, but not for sequence.

Table 6. Summary of Standard Deviation of Speed (SDS)

	Placebo (N=40)	ZST 4h (N=40)	ZST 3h (N=40)	ZOP (N=39)	
SDS (km/h)					
Mean (SD)	1.84 (0.42)	1.99 (0.53)	1.92 (0.51)	2.00 (0.42)	
Median	1.89	2.04	1.92	2.02	
Min, Max	1.00, 2.69	0.85, 3.05	0.82, 3.19	0.84, 3.06	
ANOVA Analysis					
LS Mean (SE) treatment	1.83 (0.08)	1.98 (0.08)	1.91 (0.08)	1.99 (0.08)	
LS Mean (SE) difference from placebo[1]		0.15 (0.06)	0.08 (0.06)	0.16 (0.06)	
95% CI of LS difference from placebo[1]		0.03, 0.27	-0.05, 0.20	0.04, 0.29	
P-value[2] (df) treatment group difference		0.0145 (113)	0.2179 (113)	0.0096 (113)	
Treatment					0.0323 (3, 113)
Period					0.0499 (3, 113)
Sequence					0.5682 (23, 16)

Note: analysis was based on reported data as available for all subjects

1 LS Mean group difference is Treatment Group (ZST 3h, ZST 4h, ZOP) – Placebo. ZOP is combined from ZOP 3h and ZOP 4h. Placebo is combined from Placebo 3h and Placebo 4h.

2 P-value is based on ANOVA model with fixed effects for sequence, period and treatment (Placebo, ZST 4h, ZST 3h, and ZOP), a random effect for subject within sequence, and assuming compound symmetry covariance structure; the p-values are reported from LS Mean difference between Treatment Group (ZST 4h, ZST 3h and ZOP) and Placebo

Source: Study Report, Study ZI-18, based on Table 14.2.3-2, p. 68

The placebo group would be expected to have the lowest mean SDS (least speed variability), but that was the case for only 12/39 (31%) of the subjects. By contrast, ZOP was the lowest mean SDS for 9/39 (23%) of the subjects. ZST 4h was the lowest for 6/39 (15%), and the highest for 14/39 (36%). Only 39 were included in the SDS analyses due to a technical problem in recording velocity in one driving test.

In short, SDS analysis does not appear to be a useful indicator for impairment in the driving trials of ZI-18. Since the driving was conducted on open highway, rather than under controlled conditions, the results are not surprising, or of much concern.

Sub-group evaluation of "impaired" drivers in the primary endpoint results:

The subjects that were designated "impaired" at the t*=2.5 cm SDLP threshold (primary endpoint) were isolated in this review to determine whether their driving performance was consistent in the other driving tests. If the increased lateral sway in driving, or speed deviations were due to sensitivity to the medication, then they should be increased with zolpidem driving at 3 hours post-dosing, and with zopiclone, but should not be "impaired" when in the placebo arm. On the other hand, if there was evidence of

increased lateral sway or inconsistent driving speed while participating in each of the trial arms, then it could be attributed to poor driving technique irrespective of the medication. Table 7 summarizes the lateral sway and driving speed deviation for the 5 subjects that were designated "impaired" drivers (mean SDLP t*=2.5 cm) in the primary endpoint assessment.

Table 7. Comparison of ZST 4h "impaired" drivers (SDLP t*=2.5 cm) to performance in other trial arms.

Subject #/ test/ threshold max.	ZST 4	ZST 3	ZOP	Placebo
	Mean 16.7	Mean 17.3	Mean 18.3	Mean 15.9
09 (2.5 cm)				
SDLP	19.03	17.41	21.10*	16.46
SDS	2.28	2.04	3.06*	2.13
22 (2.75 cm)				
SDLP	14.60	12.87	13.26	11.64
SDS	1.69	1.24	1.52	1.23
10 (3.0 cm)				
SDLP	21.70	25.23*	21.78*	18.59
SDS	2.61	2.51*	1.86*	2.02
35 (3.75 cm)				
SDLP	26.16	26.20	22.78	22.17
SDS	2.16	1.93	2.13	1.82
25 (6.5 cm)				
SDLP	18.22	14.06	12.55	11.72
SDS	1.82	1.62	1.82	1.76

* = early termination of driving test due to driver falling asleep
Clin. Review chart, Davis

Of the 5 subjects in the "impaired" group by primary endpoint evaluation, 4 of the 5 registered SDLPs larger than the mean (16.7 cm) for the ZST 4h group. Subject # 22 had a SDLP score lower than the group mean, but significantly larger than when driving in the placebo group, however, comparison of the ZST 4h score to performance while driving in the ZST 3h or ZOP groups indicates that the largest score for driving sway occurred while in the ZST 4h group. Similar inconsistency was noted in the driving of subjects #25 and # 35, where SDLP scores were better when driving in the ZOP group compared to the other active treatment groups. For subjects # 22 and 25, the SDLP score while in the ZST 4h group was the highest recorded during all their driving trials; for both subjects the highest scores occurred during their last (4^{th}) driving trial. A period effect was not noted for the others in the group of 5.

Two of the 5 subjects in the "impaired" group (by primary endpoint evaluation) had an early termination due to falling asleep (one in the ZST 3h, and both in the ZOP groups). Both subjects (3 009 and 010) are 23 year old white females. Of possible concern is the

SDLP score for subject # 010 which indicates that the SDLP score prior to termination in the ZOP group was quite similar to the score while in the ZST 4h group suggesting that decrement in performance may not foreshadow sudden onset of sleep.

Comparison of SDS scores for the 5 subjects between active treatment and placebo does not suggest any pattern or consistency.

Safety Endpoints/Summary:
The safety review for the driving trials involved only single-dose exposures to the active treatment drugs (twice to zolpidem SL 3.5 mg, and once to zopiclone). The primary focus of the safety review was the possible residual sedation effect. Three (3) driving tests were terminated prematurely, in 2 subjects, considered by the instructor too drowsy to drive safety (recorded as: subject fell asleep during driving). Two of the driving tests followed ZOP administration (terminated at 70 min, and at 43 min), and one followed ZST 3h (terminated at 44 min). Somnolence was the most frequently reported TEAE with 7 reports from 6 subjects (2 each during ZOP, ZST 4h and ZST 3h treatment, and one during placebo treatment). Also, there were 2 reports of fatigue from 2 subjects (both during placebo treatment), and 3 cases of headache (one each during ZST 4h, ZST 3h, and one during placebo treatment).

All AEs reported rated as mild, except one case of moderate nausea (subject 0008) after treatment with ZST 4h. Onset was reported as 22.5 hours after dosing with ZST, and lasting 17 hours. Symptoms resolved following a single dose of 500 mg paracetamol.

Overall, AEs were reported by 14 of the 40 subjects (35.0%). Three of the AEs occurred prior to dosing. TEAEs were reported by 5 subjects each in the placebo, and both of the zolpidem groups, and by 7 subjects while in the zopiclone group. There was no clear relationship between treatment and the percentage of subjects reporting AEs.

Looking at the subjects with complaints of somnolence (sleepiness/tiredness) on zolpidem, the one driver in the ZST – 4 hour (subject # 0001) group had an SDLP from placebo driving of 1.9 cm. There were 3 subjects in the ZST – 3 hour group, subjects 0006, 0007, and 0010, with differences in SDLP from placebo driving of 1.2 cm, 3.1 cm, and 6.6 cm, respectively. Subject 0010 also had complains of somnolence on ZOP and the SDLP difference from placebo was 3.2 cm; however, while on the ZST 4h arm, the SDLP difference was 3.1 cm without a complaint of somnolence.

Review of screening and follow-up labs, ECGs, and concomitant medications lists showed a few abnormalities not considered clinically significant. The only largest change in labs was noted for urinary ketones. Ketones were reported as positive at follow-up, but not at screening, in 8 subjects (20.0%) of subjects, and positive at both screening and follow-up in1 subject (2.5%).

Efficacy Summary:
The sponsor has submitted a well-designed and conducted highway driving trial for evaluation of early morning functioning (PD), following MOTN of zolpidem SL 3.5 mg.

Commencement of driving was judiciously timed to coincide with the minimal period following zolpidem SL 3.5 mg dosing (4 hours), if used as directed, and an additional treatment arm added for evaluation an hour earlier (at 3 hours). The comparison treatment arms were zopiclone at 9 hours post-dosing, and placebo. The results of this trial are a welcome addition to the knowledge base on the insomnia medications which has not previously had driving studies conducted near the time of awakening time.

Overall, drivers in the ZST 4h arm recorded a slightly increased sway compared too driving on placebo, but less than when driving in the ZST 3h group, and the zopiclone, as expected, showed the largest deviation, although not consistently, which reflects on the amount of "noise" inherent in driving trials. Each driving evaluations lasted ~ an hour. Terminations due to "driver falling asleep" occurred twice in the zopiclone group, once in the ZST 3h group, but not in the ZST 4h, or placebo groups.

To discuss the Sponsor's driving test conclusions, the Sponsor's comments have been placed in italics for ease of comparison to review comments:

SDS, which is not a primary measure in the literature, showed inconsistent results in that mean difference between zolpidem and placebo speed control was not statistically significant.
Variation in speed was analyzed, but not found to have any predictable changes attributable to treatment arm, or to the SDLP scores.

The results of the symmetry analysis indicate that when driving began 4 hours after taking ZST there were no statistically significant next morning effects on SDLP at any of the tested thresholds. When driving commenced 3 hours after taking ZST, the symmetry analysis showed statistically significant drug effects on driving performance in subjects up to and including the 4.0 cm threshold.
This review does not consider the symmetry analyses pertinent to the data evaluations.

The analysis of mean differences in SDLP showed a statistically significant difference of 0.8 cm between ZST 4h and placebo. The magnitude of this difference is small and well below the 2.5 cm primary critical value utilized in this study. These results combined permit us to conclude that when taken as directed, ZST does not cause impaired driving. The mean difference in SDLP between ZST 3h and placebo was 1.5 cm, which was also statistically significant. The difference, however, is small and is below the 2.5 cm critical value. When taken 3 hours before driving, ZST would be expected to produce some effects on next morning driving performance.
At the end of the review cycle, we were left with concerns as to the significance of driving sway. The designation of "impaired" for the ZI-18 trial is based on the 2.5 cm threshold, which has previously been used in driving trials, but has not been validated in a way that would allow correspondence of a threshold level to a known driving risk increase. It is difficult to know what importance to attach to a mean SDLP of 2.5 cm over the course of the driving test when for all the groups. The LS mean difference from placebo is 0.8 cm for zolpidem 3.5 mg at the 4 hour post-dosing driving, a very small change. The zopiclone group recorded a LS mean difference of 2.5 cm from placebo (at

the borderline for the "impaired" designation), which is a 1.7 cm difference from the mean for ZST 4h. There is currently no good measure for the significance to attach to any amount of change from placebo, but the mean 0.8 cm shift for ZST 4h suggests a successful finding for the trial. However, those results deal with only the mean values for the study. The questions remain regarding the performance of individuals that might be more sensitive to the effects of the medication. For the primary endpoint of SDLP t*=2.5 cm for ZST 4h driving, if using the sponsor's symmetry analysis, again the trial would appear to be successful. But if looking at the individuals exceeding the primary endpoint SDLP threshold, this reviewer would consider 5 subjects (12.5%) to be problematic and unacceptable without reassurances as to the risks involved.

The Sponsor's argument is that the "outliers" represent an expected statistical variability. Even if looking at the upper SDLP threshold level of t*= 3.5 cm set by the sponsor, 2 of the 40 subjects (5%) in the ZST 4h group would be designated "impaired", and one (2.5%) showed SDLP t*= 6 cm. There was not enough data to aid in determining if there were characteristics of the "outliers" to allow any predicting of who might possibly be at increased risk. The sponsor was requested as part of the CR response to provide additional PK and PD data culled from the earlier trials during the drug development. The sponsor's submission of the PK and PD summaries was done May 26, 2011, and the review of the summaries is presented in the following sections.

5. Possible relationship between PK profile, pharmaco-dynamic differences, and demographic variables

5.1 Overview

In the previous cycle review of zolpidem SL 3.5 mg, there was evidence that the plasma concentration at 4 hours (C_4) post-dosing (mean = 26.69 ng/mL) was slightly higher than the available data for plasma concentration levels for the reference drug Ambien 10 mg at 8 hours post-dosing (mean = 23.76 ng/mL). Additional assurance from the Sponsor was requested that plasma concentrations after final awakening do not result in residual effects. Trials during the development of Intermezzo using PK endpoints suggested considerable variability even in healthy young volunteers, especially in drug clearance (t½). Similar observations on PK variability were noted in the literature of the sedative-hypnotic drugs (Greenblatt, et al. 1998, 2000). Specifically in question was whether higher C_4 levels of Intermezzo at 3 or 4 hours post-dosing could potentially affect PD performance (i.e., driving). Also, whether females tended to have larger AUC and delayed clearance, and if so, whether the difference was attributable to lesser body weight, and whether the differences by gender analyses were reflected in PD changes.

The sponsor submitted data from the clinical pharmacokinetic studies listed in Table 8 involving a total of 148 young volunteer subjects (aged 21-59 years) - 85 males and 63 females. Study ZI-14 also included 23 elderly volunteers (aged 64-83 years), but these subjects were not included in the current analyses since the 3.5 mg zolpidem SL tablet was not recommended for the elderly population. The sponsor preferred to have the trials considered separately due to potential differences among study populations, and the

request is acceptable for this review. The sponsor stated that in only two of the studies (ZI-05-009, and ZI-17) were pharmacodynamic measures were obtained concurrently with blood sampling. However, the individual data sets for the ZI-16 trial suggest that enough data is available, and the PK/PD results have been included in this review. Including the PK and PD data from ZI-16 increases the subject total to 95 males and 81 females.

Table 8. Trial data included by Transcept Pharm. in the May 26, 2011 submission.

Study	Number of Subjects		Pharmacodynamic data
	Male	Female	
ZI-05-009	13	11	Yes
ZI-13	13	19	No
ZI-14[a]	15	9	No
ZI-15	18	14	No
ZI-16[b]	10	19	Yes
ZI-17	26	9	Yes

a: Elderly subjects (n=23) were studied as well as the 24 non-elderly subjects.
b: Sponsor states "Not included in the full pharmacokinetic analyses, since only two plasma concentration points were available".
Source: (b) (4) Study Report, May 26, 2011, Part 1, p. 7

The sponsor proposed the following for their reviews of the data:

- In each of a series of pharmacokinetic studies included in the clinical pharmacology section of the NDA, to identify the individual subjects in the top 10_{th} percentile of the observed distributions of C_{max}, C_4, and total AUC.
- In studies incorporating both pharmacodynamic and pharmacokinetic endpoints, evaluate the extent to which PK and PD outliers correspond--that is, whether individuals with high systemic drug exposure are the same as those with the greatest pharmacodynamic response

Transcept compiled a top 10^{th} percentile list (i.e., "outliers") for each of the trials that included PD and/or PK data (Table 9). However the Sponsor cautioned that "*Within each study, between-subject variability in pertinent kinetic variables for zolpidem (measured as %CV) are not excessive, generally falling in the range of less than 50%. This is consistent with CV values reported in previous studies of orally-administered zolpidem. Therefore the present analysis of individuals in the top 10_{th} percentile of distributions does not represent an evaluation of "outliers" as usually understood, but rather are components of the expected between-subject variability.*"

Table 9. The 10th percentile subjects included in the Transcept PK "outliers" review.

	Gender	Age	Weight	Race	C_{max}	C_4	AUC
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
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
10th 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

Source: Source: (b) (4) Study Report, May 26, 2011, Part 1, Part 1, pgs.10-11.

The first noticeable characteristic of the population listed in Table 8 is the over-representation of females. The majority of the "outliers" are female (20/25, 80%) in all studies except ZI-17.

Using the top 10th percentile individuals for each trial seems to lose some of the information on individual PK levels. Included are only 2 to 3 subjects per trial while providing no insights on the frequency or range of the higher deviations from the mean.

In this review, the inclusion for "outliers" data collection was shifted to all individual with plasma concentration (C_4) levels >30 ng/mL at 4 hours post-dosing of zolpidem SL 3.5 mg. The >30 ng/mL level is an arbitrary choice, but is a level higher than the mean for most of the Intermezzo trials, or for Ambien 10 mg, so it can serve as a starting point for evaluation of elevated PK. The subjects with elevated C_4 zolpidem levels that were included in the sponsor's top 10th percentile list subjects are marked by an asterisk (*) in my review charts below. The charts for the 6 trials list the subjects with elevated plasma concentration at 4 hour post-dosing of zolpidem SL 3.5 mg, but also include the C_4 levels at 5 hours. The assumption is that the earliest time point at which individuals would probably be driving, if Intermezzo is used as recommended, is somewhere between 4 and 5 hours post-dosing, or at some point not far past 5 hours.

5.2 Trials with PK Data – ZI-13, ZI-14, ZI-15

Trials ZI-13, ZI-14, and ZI-15 collected pharmacokinetic data without corresponding pharmacodynamic data. The submitted PK/ PD data summaries contained graphs and tables, but did not include discussion of the individual PK trials. The summaries are presented in Table 8 above. See Sponsor's conclusions at the conclusion of this section.

Trial ZI-13
ZI-13 was a 2-sequence bridging trial of 2 formulations of zolpidem 3.5 mg SL, comparing the IND formulation to the proposed commercial formulation. Table 9 lists the subjects with plasma concentrations of zolpidem >30 ng/mL at 4 hours post-dosing. The trial mean in the chart is for the proposed commercial product. By comparison, the mean plasma concentration of the IND formulation at 4 hours was 25.8 ng/mL, and at 5 hours, 17.2 ng/mL, slightly lower than the commercial formulation at both time periods.

Note: the subject numbers and PK data in Table 8, the Sponsor's PK top 10th percentile, do not correspond to the data sets submitted in the original NDA submission. Since data sets were not submitted with the May 26th, 2011 PK/PD analyses, comparisons cannot be made. Also, the C4 trial mean is listed as 29.3 in the original data summary with the NDA submission, but the recent demographics submission lists the mean C4 as 38.7 ng/mL for males, and 48.3 ng/mL for females. The original data sets have been used for the review Table 10.

The Z-13 trial included 32 subjects (13 males and 19 females). The list of subjects with elevated C_4 at 4 hours post-dosing (Table 9), includes 12 subjects, 37.5% of the trial

population at >30 ng/mL, 6 subjects (18.8%) at >40 ng/mL, 2 subjects (6.3%) at > 50 ng/ml, and 1 subject (3.1%) at > 60 ng/mL.

Ten of the 12 subjects on the >30 ng/mL list at 4 hours post-dosing are female (10/19, 53% of the female enrollees). All 5 of the subjects on the list with C_4 >40 ng/mL are female. Half of the females on the list were above the mean body weight for females in the trial, and half were below, and it is a similar difference for the two males on the list. The subject (# 106) with the highest C_4 was below the mean for both body weight and BMI. So, in general, body weight and BMI do not sizably account for the gender difference in elevated PK levels.

Of note is that half of the subjects with C_4 > 30 ng/mL at 4 hours retained the elevated level at the 5 hour mark, although all had C_5 <40 ng/mL.

Table 10. Subjects with elevated plasma conc. at 4 hour post-dosing – Protocol ZI-13.

Gender, age, race/ethnicity, subject ID	Plasma conc. at 4 hours (ng/mL)	Plasma conc. at 5 hours (ng/mL)	Wt. (kg.)	BMI (ng/m^2)
	mean 29.3	mean 18.8	M mean 78.6 F mean 68.2	mean 24.9
F 36 W 112	30.2	17.2	54.2	21.7
F 43 W 108	30.6	16.1	78.7	27.6
F 47 W 126	35.7	23.9	72.9	28.1
M 20 W 107	35.9	15.7	70.0	21.6
F 23 W 111	35.9	19.8	66.9	21.5
M 52 AA 109	39.1	30.2	81.6	27.6
F 25 W 118	40.6	29.2	60.4	21.4
F 51 W 113*	44.1	31.0	84.9	29.7
F 36 W 128	45.0	31.2	70.1	24.8
F 40 U 103*	45.4	34.6	69.2	29.5
F 20 W 123*	50.3	34.9	66.8	29.3
F 28 W 106*	63.4	39.1	58.4	19.5

* = included in the Transcept top 10th percentile analyses
U=unknown
Source: Clin. Review chart, Davis

Since there is a slight difference in the plasma concentration means for the formulation used in the INDs and the proposed commercial formulation, it seemed worthwhile to view the comparisons. As seen in Table 11, there is a slightly longer t½, and AUC, but the differences are small, and not considered significant.

Table 11. ZI-13 Comparison of Commercial and IND formulations

Summary of Pharmacokinetic Results-Zolpidem (N = 32)

Parameters		Proposed commercial formulation 3.5 mg sublingual zolpidem tartrate lozenge (A)			IND formulation 3.5 mg sublingual zolpidem tartrate lozenge (B)		
		Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	215.51	74.63	34.63	197.74	70.83	35.82
AUC_{0-inf}	(ng·h/mL)	253.56	113.51	44.77	233.74	111.44	47.68
$AUC_{t/inf}$	(%)	87.70	7.33	8.36	87.88	7.98	9.08
C_{max}	(ng/mL)	62.93	21.51	34.17	60.44	19.04	31.50
T_{max}	(h)	0.933	0.436	46.77	0.742	0.396	53.38
T_{max}*	(h)	0.858	0.500	-	0.667	0.333	-
K_{el}	(h^{-1})	0.3201	0.0952	29.73	0.3162	0.0871	27.55
$T_{½ el}$	(h)	2.36	0.73	30.85	2.40	0.88	36.62

* Medians and interquartile ranges are presented.

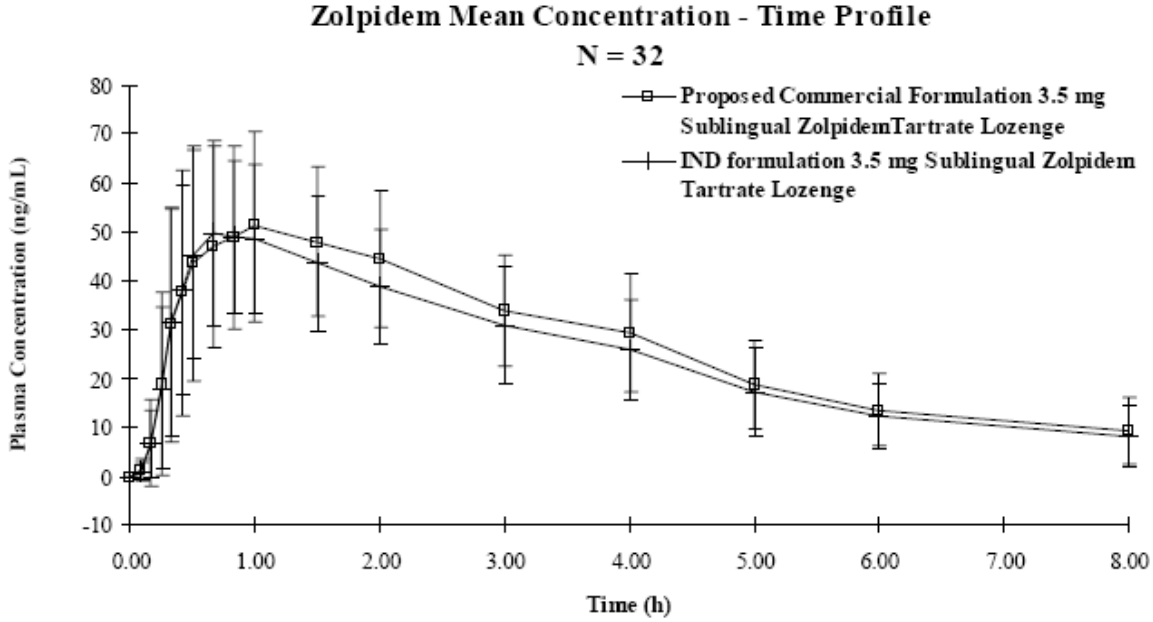
Proposed Commercial Formulation 3.5 mg Sublingual Zolpidem Tartrate Lozenge (A) vs IND Formulation 3.5 mg Sublingual Zolpidem Tartrate lozenge (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.05%	109.16%	102.94%
90 % Geometric C.I.[2]	103.36 % to 115.06 %	103.33 % to 115.33 %	93.95 % to 112.78%
Intra-Subject CV	12.69 %	13.00 %	21.78 %

1 Calculated using least-squares means according to the formula:
e(Proposed commercial formulation 3.5 mg sublingual zolpidem tartrate lozenge (A) - IND formulation 3.5 mg sublingual zolpidem tartrate lozenge (B)) X 100
2 90% Geometric Confidence Interval using ln-transformed data
Source: Study Body Report, ZI-13, Section 4.2

Fig. 3 displays the differences visually indicating that a slight difference in PK levels are present at the 4 hour post-dosing time point when comparing the formulations, with the commercial formulation slightly higher at most time points past C_{max}.

Fig. 3. Comparison of the IND and commercial formulations of zolpidem SL 3.5 mg.



Source: Trial ZI-13 Report Body, Section 14.2.2, p. 96

Trial ZI-14

Trial ZI-14 was an open-label, single-dose cross-over trial PK trial comparing the 3.5 mg and 1.75 mg dose strengths of zolpidem SL in elderly and non-elderly subjects. Overall, at 4 hours post-dosing, 7 (29.2%) of the 24 adult non-elderly subjects involved in the trial had plasma concentrations of zolpidem >30 ng/mL (Table 12). Three subjects (3/24, 12.5%) had levels >40ng/mL, and 1 subject (4.2%) had a level >50 ng/mL.

Although the "outliers" table includes several males, they represent 20% of the male population in the trial, compared to the females "outliers" who represent 44.4% of the females group in the trial. At 5 hours, only 2 of the subjects, 1 male and 1 female, had plasma conc. levels < 30 ng/mL, while the other 5 (20.8% of the non-elderly group) remained with elevated PK level. Looking at body weight, two of the females are above the trials mean body weight for females, and two above (but those are the two with higher C4 levels). Two of the three males were above the trials mean for body weight. Gender, but not body weight, BMI, age or race/ethnicity appears related to the elevated C4 levels

Of the subjects with elevated plasma concentration levels at 4 hours, 5 of the 7 (5/24, 20.8% of the total trial population) remain elevated at 5 hours. This includes one subject each with C_5 >40 ng/mL, and C_5 >50 ng/mL.

Table 12. Subjects with elevated plasma conc. at 4 hour post-dosing - ZI-14.

Demographic Gender, age, race/ethnicity	Plasma conc. at 4 hours (ng/mL)	Plasma conc. at 5 hours (ng/mL)	Wt (kg.)	BMI (kg/m^2)
			m = 84.9	m = 27.5
F 46 W 001	30.9	23.0	76.4	28.0
M 40 AA 002	35.5	28.7	94.5	29.0
M 31 W 028	38.2	32.6	84.0	27.3
F 40 AA 006	39.9	36.2	93.2	33.1
M 28 AA 011*	45.5	42.5	93.2	27
F 34 W 045	45.7	37.3	62.7	23.0
F 42 W 017*	51.2	50.4	70.0	23.4

* = included in the Transcept top 10^{th} percentile analyses
Source: Clin. Review chart, Davis

Trial ZI-15

Trial ZI-15 evaluated zolpidem SL 3.5 mg under fasted and fed conditions, and Ambien 10 mg. Using the fasted data, probably most typical for individuals in the middle-of-the-night, 12 of the 32 enrolled subjects (37.5%) had plasma concentration levels >30 ng/mL at 4 hours post-dosing, and 10 of the 12 were females. Three subjects had C_4 > 40 ng/mL, and one > 50 ng/mL. Three subjects still had plasma concentration levels >30 ng/mL at 5 hours (3/32, 9.4% of the trial population), but all were < 40 ng/mL. (Table 13).

Evaluation of the data by body weight and BMI does not show any clear relationship. Six of the 10 females on the list, and 1 of the 3 males had body weights below the trial mean by gender. Looking at the top 10^{th} percentile subjects, 2 of the 3 were above the mean, although, again, the subject with the highest C_4 was female and below the mean trial body weight.

Table 13. Subjects with elevated plasma conc. at 4 hour post-dosing – Protocol ZI-15.

Demographic Gender, age, race/ethnicity	Plasma conc. at 4 hours (ng/mL)	Plasma conc. at 5 hours (ng/mL)	Wt. (kg.)	BMI (kg/m^2)
	Top = Fasted, m = 26.7 (R = 6.8-55.4) Lower = Fed, m = 24.5 (R = 12.3-49.3)	Top = Fasted, m = 17.0 (R = 2.4-38.7) Lower = Fed, m = 22.1 (R = 9.6-40.9)	mean 75.8	mean 25.4
M 27 AA 1007	27.9 39.3	22.1 32.7	79.9	23.3
F 24 AA 1006*	34.8 38.3	22.0 31.6	67.9	23.8
F 54 W 1008	35.1 28.2	27.7 35.6	64.8	25.0
F 34 W 1021*	35.2 29.2	26.4 32.2	61.5	21.4
F 58 W 1011	35.5 28.9	19.8 27.0	67.0	23.7
F 27 W 1024	36.3 35.3	25.9 29.2	81.8	30.8
M 31 W 1026	37.6 31.0	25.1 29.8	87.2	32.1
F 51 AI 1031	38.1 30.5	23.2 29.1	58.0	22.4
F 22 AA 1012	38.3 32.1	23.9 28.1	80.7	27.9
F 59 W 1004	39.6 21.8	30.4 22.0	83.3	30.5
F 49 W 1005*	46.3? (3h = 32.2) 17.4	18.1 17.4	73.0	27.1
M 30 AA 1023*	46.8 49.3	37.2 40.9	90.5	30.6
F 21 W 1017*	55.4 31.0	38.7 30.5	50.7	20.2

* = included in the Transcept top 10^{th} percentile analyses
AI = American Indian
Source: Clin. Review chart, Davis
Note: sponsor listed 32 subjects for ZI-15 (18 males, and 14 females), but complete data sets were found for 36 subjects (21 males, and 15 females). The 36 subjects were included in this reviewer's charts. Comparison of subjects used in the sponsor's review to the submitted data in the original NDA application to determine which subjects were excluded in the sponsor's May 26, 2011 summaries could not be done, since complete data sets were not included in the May, 2011 submission.

General conclusions for the 3 PK-only trials will be included in the conclusions section for the PK and PK/PD trials in order to include the PK data of the additional 3 trials in the discussion of pharmacokinetic findings.

5.3 Trials with Both PK and PD Data

The next three trials provided pharmacodynamic data (PD) along with PK data. The relationship of an elevated PK level to pharmacodynamic results was difficult to ascertain

since trials during drug development that included the PK/PD relationship generally used the Digit Symbol Substitution Test (DSST). The DSST has been used in numerous trials of hypnotic medications for insomnia treatment to evaluate possible next-morning residual effects. Due to the extremely quick administration time (90 seconds or 3 minutes) and simplicity, the test is not an ideal candidate for PD evaluation. Trial ZI-05-009 also included other PD assessments, but these had the same short-comings. The tests do not adequately assess memory skills, quick higher-level decision-making, reflexes, or sustained attention in a monotonous or stimulating situation. Results on these tests did not allay concerns that after sedation for sleep, there remained the possibility of early-morning residual effects when high levels of alertness and functioning skills, such as driving, are needed.

Trial ZI-05-009

ZI-05-009 was a 4-way cross-over trial to evaluate 3 dose strengths (1.0 mg, 1.75 mg, and 3.5 mg) of zolpidem SL tablets on daytime sedation in 24 healthy volunteers (13 males, 11 females). Study drugs were administered on 2 successive days for each treatment period (washout of 5 -12 days between). The PD effects of zolpidem tartrate SL compared to placebo were investigated using the Digit Symbol Substitution Test (DSST), Choice Reaction Time (CRT), Symbol Copying Test (SCT), self-rating of sedation on a Visual Analog Scale (VAS), and the Buschke Memory Recall Test. Only the DSST has consistently been used in insomnia trials. The other PD measurements have the same short-comings, and do not add any new insight to augment the use of the DSST.

The sponsor evaluated the length of time that statistically significant differences in scores persisted for each of the difference measurements, and dose strengths (Table 14). Using the means for each group, statistically significant effects did not persist to the 4 hour mark. The longest group mean was for the 3.5 mg dosage on the number of CRT errors (3 hours). Subjects rated themselves as feeling increased sedation on the VAS for 2 hours, even for the 1.75 mg strength, compared to baseline ratings.

Table 14. PD results for 3 dosage strengths of zolpidem SL- Study ZI-05-009

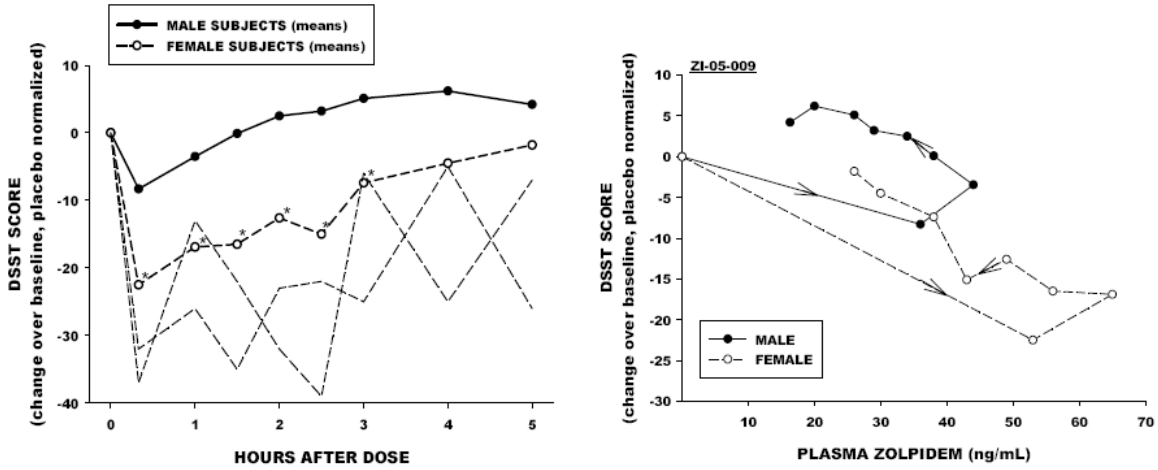
Dose	DSST*	CRT*			BMR*	SCT*	VAS*
		change in mean rxn time	# lapses	# errors			
3.5 mg	1 2 3	1 2 3	1 2 3 4	1 5	1	0	1 2 3 4
1.75 mg	1 2 3	1	1	0	0	0	1 2 3 4
1.0 mg	0	0	0	2	0	0	0

*Results significantly different from placebo at post-dose time of: 1 = 20 min., 2 = 1 hr., 3 = 1.5 hr., 4 = 2 hr., and 5= 3 hr. 0 = no significance difference from placebo at any post-dose testing time
Source: Trial report study ZI-05-009, Section

Fig. 4 presents the mean DSST change (from baseline, placebo-normalized) by gender; by time (hours) on the left, and by plasma conc. on the right. DSST scores for the males are back to baseline by hour 4, but the scores for females remain below baseline levels.

The two extra line plots are only the 2 DSST "outliers" (subject # 1902 and 1918, both female) in the figure on the left. Subject 1902 did not have an elevated C_4 at 4 hours, but subject# 1918 had an elevated plasma concentration level (not one of the highest), and a significant decrease in DSST scores at hours 4 and 5, although body weight and BMI were not below the study mean. Analyses by body weight and BMI did not indicate relationships that would account for the observed gender differences in elevated PK levels.

Fig. 4. Mean DSST profile and DSST-plasma concentrations by gender - ZI-05-009.



Left: Mean placebo-normalized DSST change scores among men and women (ZI-05-009). Asterisk (*) indicates a significant difference from zero change. Also shown are the plots (dashed lines) for the top 10th percentile subjects. Right: Relation of mean plasma concentration to mean DSST change score for men and women. Arrows indicate the direction of increasing time.
Source: (b) (4) Study Report, May 26, 2011, Part 1, Section 4.1, p. 14.

The Sponsor concluded that Pharmacodynamic response to sublingual zolpidem, based on DSST scores, was greater in female subjects than 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 (Text Figure 3, 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 (Text Figure 3, right).

Two subjects (numbers 2 and 18) were identified as 10th percentile individuals from the distribution of DSST effect areas (Text Figure 3, left). Both of these individuals were white females, aged 44 and 25 years. Neither of these subjects fell in the top 10th percentile based on the pharmacokinetic analysis

Looking at the data at 4 hours post-dosing for individual subjects (in Table 14), 7 of the 24 subjects (29.2%) had zolpidem C4 levels >30 ng/mL, and 2 (8.3%) were >40 ng/mL. All but one of the subjects with elevated C4 at 4 hours was female. Five of the 7 subjects did not have a significant decrease in plasma conc. level by 5 hours.

Regarding DSST scores, all of the subjects on the list evidenced a decrease corresponding to C4, and for 5 of the 7 subjects, also at C5. The two subjects with the highest zolpidem C4 did not have the largest decline in hour 4 DSST scores, but the subject with the highest C5 had a sizable decline in hour 5 DSST and SCT scores. VAS scores of alertness (subjective responses to the question "How alert do you feel?") were inconsistent, but marked declines were recorded for some subjects.

Comparing the PD scores to the plasma concentration levels, the DSST scores consistently show a decrease at hour 4, but scores at hour 5 are more variable. Looking at the two female subjects with C_4 >45 ng/mL, there is a decrease in all the PD scores, compared to baseline, but particularly striking is the low scores on the VAS. The VAS is not a test of functioning. Subjects are asked to rate their "alertness" ("How alert do you feel right now?) on a 100 mm scale. Although 2 subjects on the list rated their post treatment VAS scores higher, the subjects with higher C_4 levels indicated declines in alertness.

Table 15. DSST scores of subjects with elevated PK level – Protocol ZI--05-009.

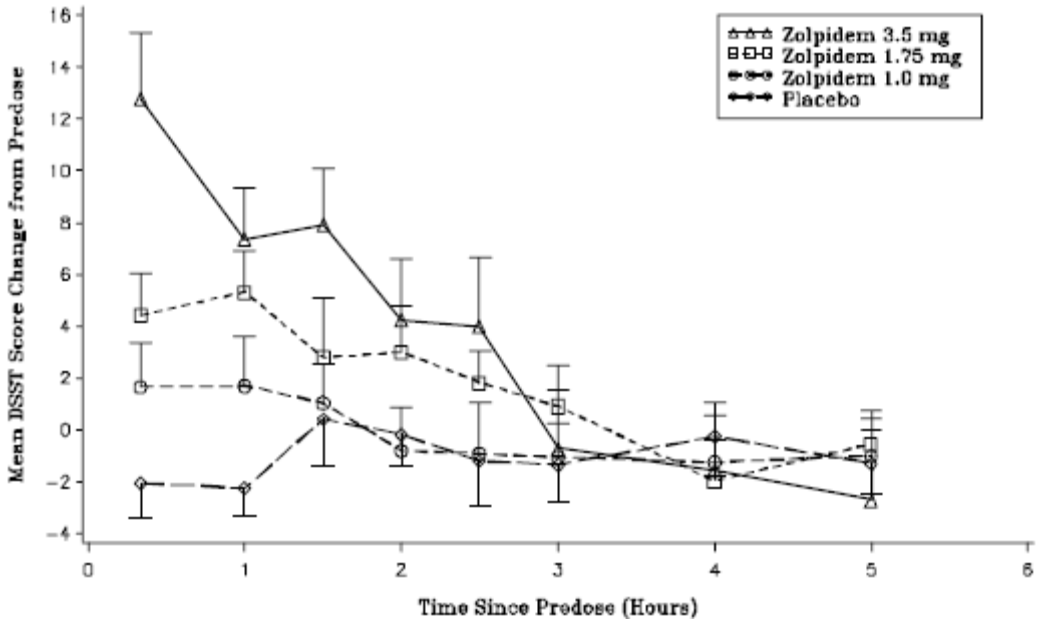
Gender, age, race/ ethnicity, subject #	Plasma conc. 4h (ng/mL)	Plasma conc. 5h (ng/mL)	Wt (kg.) BMI (kg/m^2)	DSST placebo 4h/5h ZST 4h ZST 5h	CRT (errors) placebo 4h/5h ZST 4h ZST 5h	SCT placebo 4h/5h ZST 4h ZST 5h	Buschke placebo 4h/5h ZST 4h ZST 5h	VAS placebo 4h/5h ZST 4h ZST 5h
			m=25	mP = 56.9 m4 = 58.5 m5 = 59.6	mP = 3.1 m4 = 11.3 m5 = 11.4	mP122.0 m4=126.3 m5=127.8		
F 37 W 1907	31.4	24.1	66.2 24	77/75 76 -1 79 +4	1/5 8 +7 2 -3	144/145 162 +18 162 +17	5/6 4 -1 7 +1	26/45 63 + 37 55 +10
M 26 AA 1909	31.6	30.6	87.1 26	56/55 50 -6 50 -5	0/13 3 +3 0 -13	95/117 78 -17 97 -20	4/4 5 +1 6 +2	73/71 37 -36 39 -32
F 25 AA 1918*	31.7	31.8	75.7 25	52/42 32 -20 40 -2	29/15 27 -2 16 +1	124/85 104 -20 78 -7	5/5 6 +1 9 +4	87/81 49 -38 77 -4
F 42 AA 1919*	35.4	26.5	64.0 25	80/76 70 -10 61 -15	62/53 26 -36 55 +2	155/151 139 -16 147 -4	6/7 6 0 9 +2	77/83 83 +6 93 +10
F 38 AA 1913	38.3	38.1	73.9 27	48/48 43 -5 41 -7	0/0 1 +1 0 0	104/107 97 -7 92 -15	5/3 6 +1 6 +3	70/71 29 -41 22 -49
F 38 W 1924*	46.6	40.4	67.8 30	56/61 53 -3 48 -13	65/56 37 -28 48 -8	122/123 100 -22 90 -33	6/7 6 0 4 -3	74/67 46 -28 42 -25
F 33 W 1923*	49.2	36.8	59.0 23	62/62 57 -5 65 +3	5/4 0 -5 4 0	132/141 125 -7 139 -2	6/7 7 +1 7 0	76/83 29 -47 79 -4

* = included in the Transcept top 10th percentile analyses
Source: Clin. Review chart, Davis

The mean pre-dose DSST score was 56.9 (±2.7). At 20 minutes post-dosing, the mean DSST score was 44.1, a change of 12.8 (±2.6) points, as represented in Figure 5, a

difference in LS Means of 14.8, p<0.0001. At 4 and 5 hours, the mean DSST score was slightly above the baseline score for the zolpidem SL 3.5 groups. However, the early change of 12.8 points was interpreted as evidence of sedative properties of the zolpidem by the Sponsor. Looking at subjects with elevated C_4 levels, (Table 14), one subject (# 1918) surpassed that DSST change level at 4 hours, and 2 others (subjects 1919 and 1924) at 5 hours post-dosing (all females).

Fig. 5. Mean DSST score change from pre-dose by time-point following administration of zolpidem 3.5 mg, 1.75 mg 1.0 mg, and placebo.



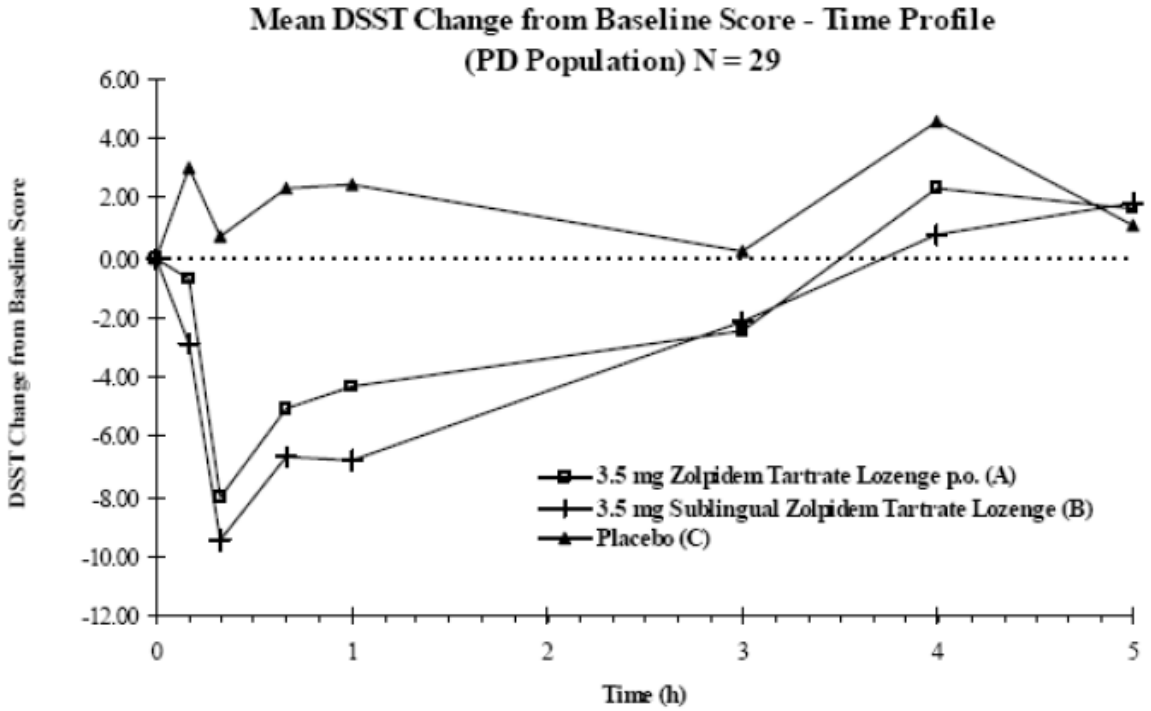
Source: ZI-05-009, Study Report Body, Section 14.2, Table 5a, and Section 14.4, Figure 1

Trial ZI-16

ZI-16 addressed the question of whether there is a difference if the zolpidem sublingual tablet is swallowed instead of dissolving in the beneath the tongue. The trial compared zolpidem SL 3.5 mg SL (dissolved), zolpidem SL 3.5 mg p.o. (swallowed), and placebo in a day-time cross-over trial that enrolled 29 healthy volunteers. During the trial, the subjects received zolpidem SL 3.5 mg twice.

Overall, the trial showed increases in the DSST scores over baseline by hour 4. DSST scores had returned to baseline (actually slightly higher) by the hour 4 measurements, but were still less than the mean placebo group score which had increased from baseline (Figure 6).

Fig. 6. Mean changes over baseline in DSST score – Study ZI-16

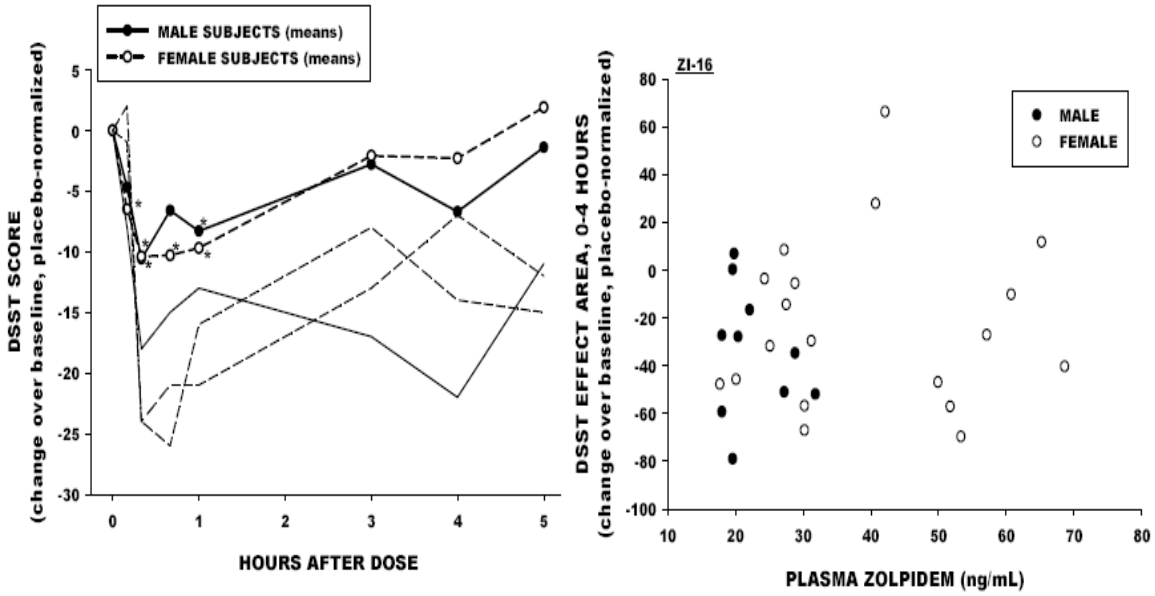


Source: Clinical Study ZI-16, Section 14

The Sponsor identified 3 subjects (# 4, 11, and 15) in the top 10th percentile for DSST changes (scores included on the Fig.4 chart on the left). None of these subjects were among the identified top 10th percentile for C3 or C4.

Figure 7 presents the DSST scores profile indicating that in this trial, by hour 4 males had lower DSST scores than females, although neither was back to baseline. The 3 extra lines are again the sponsor designated DSST "outliers", 2 females and 1 male. Subject numbers 004, 011, and 015 were included in the top 10th percentile by the sponsor. Subjects 011 and 015 did not have elevated PK levels. Subject 004 had very elevated plasma concentration levels (>70 ng/mL and >50 ng/mL on the oral and SL zolpidem 3.5 mg , respectively, but there was no significant change from baseline in the DSST scores for the higher PK level, and only slight change with the lower PK level.

Fig. 7. Mean DSST profile & DSST (AUC0-4)-4 hour plasma conc., by gender - ZI-16.



Left: Mean DSST scores for male and female subjects (ZI-16)
Asterisk (*) indicates a significant difference from zero change. Also shown are values for the top 10th percentile subjects. Dashed lines indicate female subjects; solid lines indicate males.
Right: Relation of plasma concentration at 4 hours after dosage to area under the 4-hour effect curve for DSST
Source: (b) (4) Study Report, May 26, 2011, Part 1, Section 4.2.

The Sponsor concluded*: In contrast to Study ZI-05-009, pharmacodynamic differences between male and female subjects were small, despite the gender-related plasma concentration differences at 3 and 4 hours after dosage. The area under the 4-hour effect curve was similar between males and females (mean ±SE: -28.6 ±10.5 for males, -23.1 ±8.1 for females). There was no apparent relation between C_3 or C_4 and area under the 4-hour effect curve for DSST.*

Table 16 lists the zolpidem plasma concentrations, the body weight and BMI for subjects that had a plasma conc. of $\geq$30 ng/mL at 4 hours in at least one treatment arm. The elevated C_4 list includes 13 of 29 subjects in the total trial enrollment (44.8%) The trial enrolled 10 males and 19 females, but only one male was in the high residual C_4 group (10% of the male enrollees), while 12/19 (63.2%) of the females enrollees were in that group. Four of the subjects (13.8% of the trial population) had zolpidem C_4 > 60 ng/m, and one had a level > 70 ng/mL. And at 5 hours, 3 subjects (10.3% of the trial population) had C_5 >60 ng/mL. No clear evidence for an explanation of the disproportional gender bias in the higher residual PK levels can be wholly accounted for by body weight or BMI results.

The starred subjects on the table are those evaluated by the sponsor as the "outliers", ** for the top 10th percentile in plasma conc. at 4 hours, and *** for the top 10th percentile in DSST scores changes. Of the designated top 10th percentile for PK level, subject #003 had a decline in DSST scores after oral zolpidem, but an increase after the sublingual zolpidem. Scoring for subject #005 is equally variable with generally stable or increase DSST scores except for a drop in one of the hour 5 testings. And, the third subject (#010)

had rather stable scores at 4 hour, and improved at the 5 hour testing. In the study, there does not appear to be a connection between the C_4 and PD results for those subjects with the highest residual C_4 levels.

Table 16. Subjects with zolpidem plasma conc.>30 ng/mL at 4 hour post-dosing –ZI-16

Gender, age, race/ethnicity, subject #	Plasma conc. at 4 hours	Plasma conc. at 5 hours	Wt (kg.)	BMI (kg/m^2)	Placebo DSST	DSST 4h	DSST 5h
	SL m= 3.7 p.o. m= 4.3	SL m= 30.0 p.o. m= 30.1	m = 74.0	m= 25.3	SL m=70 p.o. m=74	SL m = 70 p.o. m= 72	SL m= 71 p.o. m= 71
F 20 W 006	20.1 35.3	19.9 36.0	64.4	22.6	72 84	73 +1 79 -5	76 +4 83 -1
F 42 W*** 015	30.2 46.1	24.7 39.2	71.6	26.3	71 59	62 -9 66 +7	63 -8 65 -6
M 23 W 007	31.8 22.9	25.2 18.4	95.2	28.1	94 78	77 -17 77 -1	75 -19 76 -2
F 30 W 012	40.7 29.6	33.5 28.4	79.8	23.2	72 78	84 +12 87 +9	90 +18 73 -5
F 19 W 019	41.7 51.7	36.3 47.2	74.6	28.7	68 69	70 +2 70 +1	63 -5 68 -1
F 43 W 002	42.2 47.6	37.8 45.7	71.2	23.5	57 65	63 +6 56 -9	71 +14 58 -7
F 42 B 023	43.8 31.2	41.4 36.8	59.8	21.3	48 53	48 0 59 +6	51 +3 60 +7
F 22 W 001	49.9 57.7	48.0 46.0	65.7	24.1	72 63	70 -2 62 -1	74 +2 67 +4
F 18 W 016	50.7 57.1	43.1 57.0	64.8	23.1	78 78	67 -11 79 +1	73 -5 85 +7
F 40 B*** 004	53.3 71.4	53.7 60.0	91.6	32.1	57 57	55 -2 56 -1	52 -5 62 +5
F 31 W** 003	57.1 65.2	57.8 57.3	47.6	20.2	59 77	70 +11 67 -10	74 +15 69 +8
F 27 W** 005	68.4 60.7	69.0 58.3	69.8	24.9	59 70	58 -1 75 +5	66 +7 64 -6
F 31 W** 010	68.6 49.5	68.5 47.1	61.2	23.2	74 73	73 -1 72 -1	77 +3 75 +2

m = mean
** = top 10th percentile in plasma conc. at 4 hours
*** = top 10th percentile in DSST scores changes
Source: Clin. Review chart, Davis

The first post-dosing blood draw in ZI-16 was done at 1 hour. C_{max} in the trials with more frequent PK testing was generally at ~45 minutes. Using the 1 hour data for C_{max} for the trial, obtained from the original NDA data sets, gives a C_{max} of 65.6 (+22.5) ng/mL for the oral zolpidem 3.5 mg, and C_{max} 68.6 (+19.0) ng/mL for the sublingual tablet. The C_{max} information provided in Table 8 C_{max} 29.1 ng/mL for males, and 48.8 ng/mL for females) appears to be inaccurate.

If the sponsor provided data for C_{max} is correct, the C_4 levels for several female subjects (# 010, 005, 003, and 004), are more than double the trial mean C_{max} level for males. For the purposes of this review, the C4 "outliers" are compared to the higher dataset C_{max} levels which still indicate that 3 subjects (# 004, 005, and 010, all female) have zolpidem C_4 levels above the mean C_{max} for the trial (67.1 ng/mL, combined males and female).

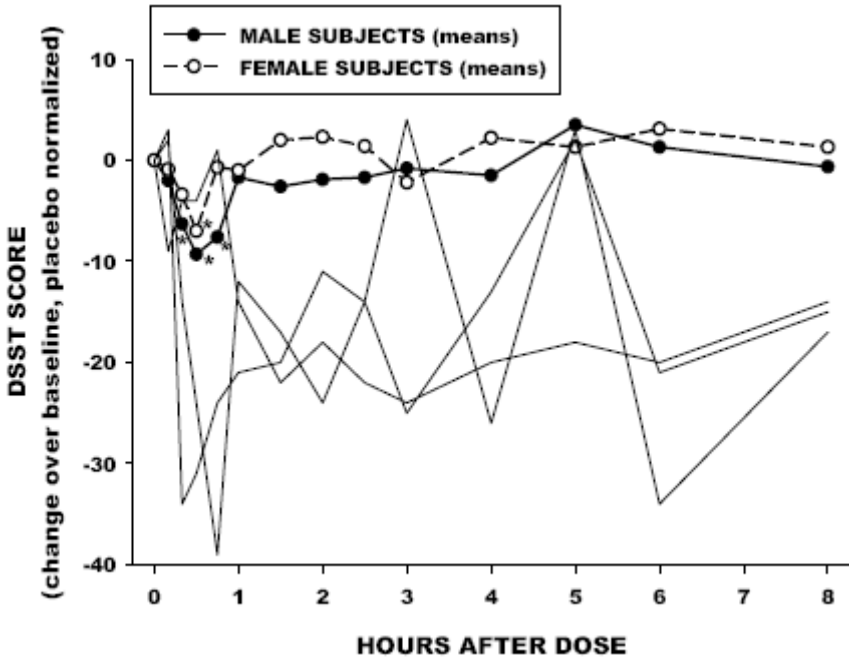
Overall, the subjects with the highest plasma concentration levels at 4 hours post-dosing did not have the most significant declines in DSST scores.

Trial ZI-17

The Transcept review included 6 subjects in the PK top 10th percentile. Also included are 3 subjects in the top 10th percentile with significant differences in DSST scores (subject # 020, 023, and 031, all males), but none of these subjects had elevated zolpidem C_4 levels (Figure 6, placebo-normalized DSST changes and the 3 DDST "outliers".

Figure 8 presents the mean (placebo-normalized) DSST change scores, by gender for trial ZI-17. The 3 extra lines are the DSST score variations for the 3 male PD "outliers", none of which had elevated PK scores. Analysis by weight, age, and race were also unremarkable.

Fig.8**.** Mean placebo-normalized DSST change scores, by gender, ZI-17.



Asterisk (*) indicates a significant difference from zero change. Also shown are the plots (solid lines) for the top 10th percentile subjects.

Source: Source: (b) (4) Study Report, May 26, 2011, Part 1, Section, Section 4.3, p. 17

The Sponsor concluded that Gender differences in pharmacodynamics were small, with male subjects actually having a slightly higher mean area under the 4 hour effect curve than women (-12.7 ±5.5 vs. -6.4 ±7.8: difference not significant).

Trial ZI-17 compared zolpidem SL 3.5 mg tablets to oral tablets of the same dosage, and to Ambien 10 mg tablets. Differences between the two 3.5 mg tablets were not significant, so the PK and PD results for both were included in this review. The trial included 26 males, and 9 females.

Overall, in this trial, the mean female PD scores were slightly higher than those of the males at 4 hours post-dosing. This was the only one of the six trials in which the mean C4 for females, 21.7 ng/mL (compared to 15.4 ng/mL for males), was below 30 ng/mL.

Only 4 of the Sponsor's list of 6 PK "outliers" is included in Table 16 since two of the subjects were "outliers" due to AUC values, but by hour 4 post-dosing their plasma conc. levels were less than 30 ng/mL (Table 17). PK data was available in the data sets for subjects 1019 and 1034, but no DSST data could be located.

Table 17. Subjects with elevated plasma conc. at 4 hour post-dosing – Protocol ZI-17.

Demographic Gender, age, race/ethnicity	Plasma conc. at 4 hours (ng/mL)	Plasma conc. at 5 hours (ng/mL)	Wt (kg.) BMI (kg/m2)	Baseline DSST	DSST 4h	DSST 5h
	Top=SL Lower=p.o. m = 17.1	Top=SL Lower=p.o. m = 12.2	m = 77.3 m = 25.0	SL m = 54.2 p.o. m = 52.6	m = 51.9	m = 51.3
M 27 AA 1030*	25.9 32.5	23.8 24.2	84.5 26.1	39 47	39 0 43 -4	42 +3 38 -9
F 37 W 1034*	28.0 38.4	22.2 28.4	73.6	Not located	—	—
F 24 W 1019*	37.5 29.7	20.6 13.6	50.0	Not located	—	—
F 22 AA 1014*	42.9 33.5	35.9 21.7	88.5 25.1	55 50	66 +11 46 -4	52 -3 48 -2

* = included in the Transcept top 10th percentile analyses
Clin. Review chart, Davis

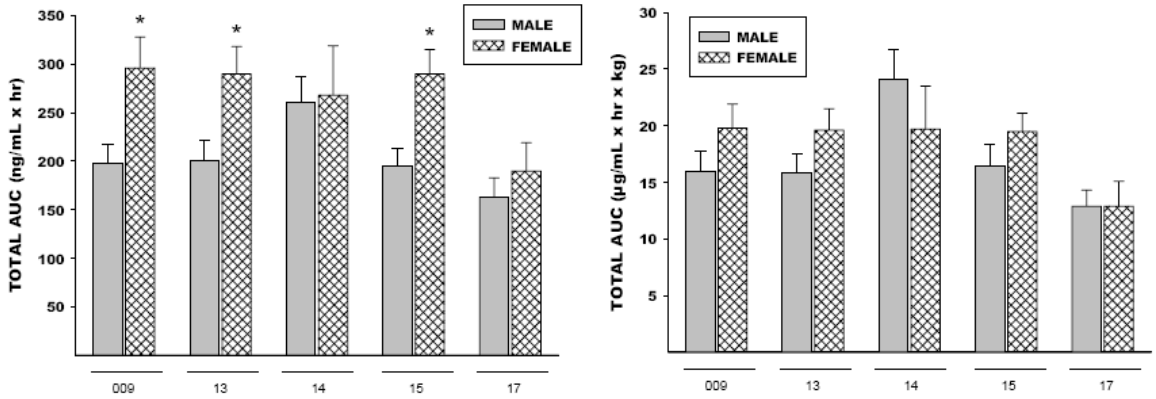
Overall, in trial ZI-17, subjects assigned to both the oral and sublingual zolpidem 3.5 mg tablet groups, on average, scored slightly lower than those on placebo at the 4 hour post-dosing DSST tests. The mean DSST score at 5 hours suggested subjects in the sublingual tablet group had scored higher than either placebo or oral zolpidem. Again, results are noted, but the effort is to avoid over-interpretation of these PD results due to the short-comings of the testing measurement.

The C_{max} listed by gender in Table 9 may not be accurate. From the original NDA submission dataset, the C_{max} for the oral zolpidem 3.5 mg appears to be 46.0 (+2.9) ng/mL, and for the sublingual tablet, 43.8 (+2.7) ng/mL. It is unlikely that the C_{max} for both males and females would be 43.8 (+2.7) ng/mL. Only one of the PK "outlier" subjects in the ZI-17 trial had C4 levels near the mean trial C_{max} (combined males and female).

Conclusions for the PK and PK/PD Trials

Sponsor Conclusions on PK data:
The data indicates gender influences the pharmacokinetics of zolpidem. Following 3.5 mg of sublingual zolpidem tartrate, women on average may have up to 50% higher systemic exposure (based on total AUC) than men. The difference is partly but not entirely explained by differences in body size. However, the differences were partly explained by body weight, inasmuch as gender differences in weight normalized variables were smaller and generally not significant. This is illustrated in Figure 8. Weight-adjustment narrows the different in AUC effect in 3 of the 5 studies, and equalizes or reverses it in one each. This is illustrated in the Figure 9 comparison of mean total AUC by gender in the first chart, and adjusted by weight in the second chart.

Fig. 9. Mean (±SE) total AUC for zolpidem for male and female subjects in five separate studies



Asterisk (*) indicates significant differences between male and female groups. Left: AUC differences are significant in 4 of the 5 studies. Right: After normalization for body weight, gender differences in AUC are no longer significant.
Source: Source: (b) (4) Study Report, May 26, 2011, Part 1, Section 3.1, p. 9

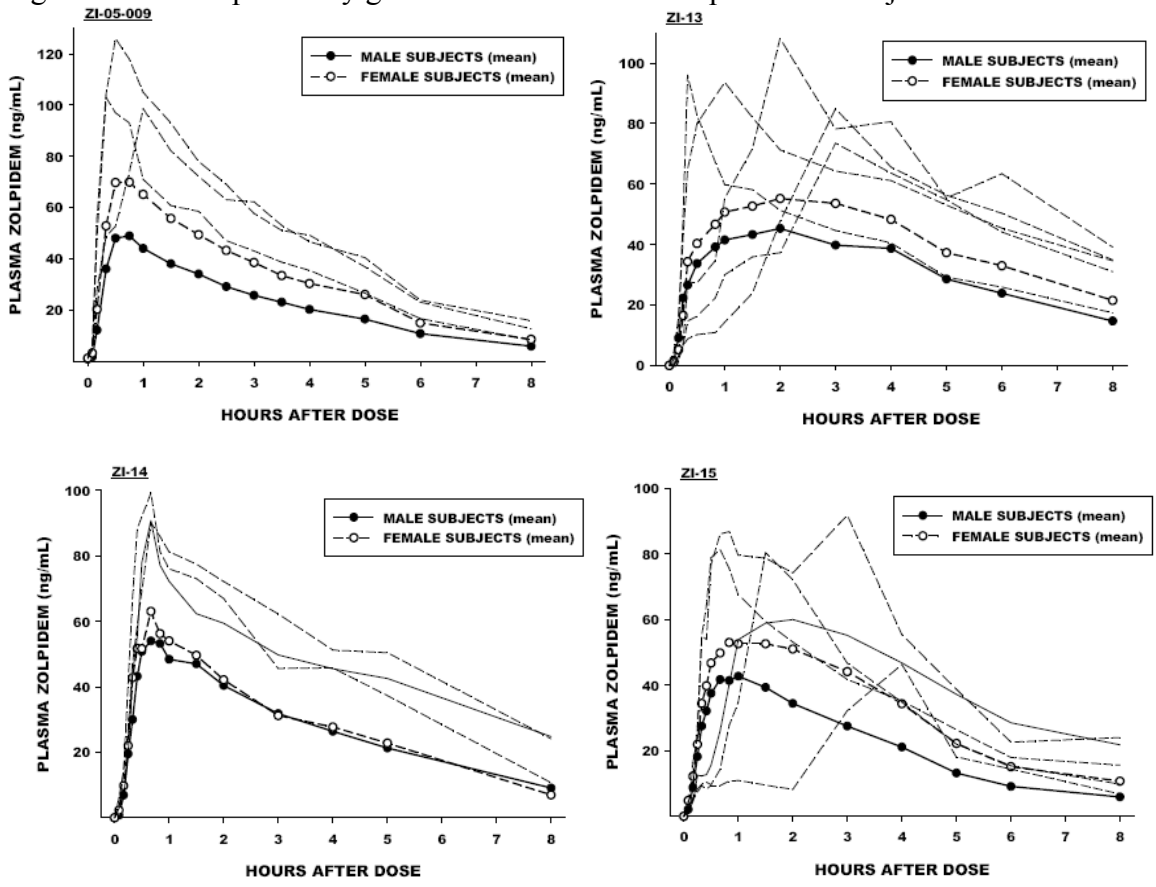
The majority of the subjects in the top 10th percentile group were female. The male-female distribution in this group (5/17, excluding Study ZI-16) was significantly different from the distribution in the overall study population (85/63) (chi-square = 12/7, p<0.001). Examination of the age and weight characteristics in the top 10th percentile group indicates no evident differences in comparison with the group means. There also was no apparent race/ethnicity relationship to 10th percentile status. None of the mean PK levels, including T ½, was consistently higher for females in the trials. Comparison by body weight, BMI, age, or race/ethnicity to the 10th percentile did not show any relationship.

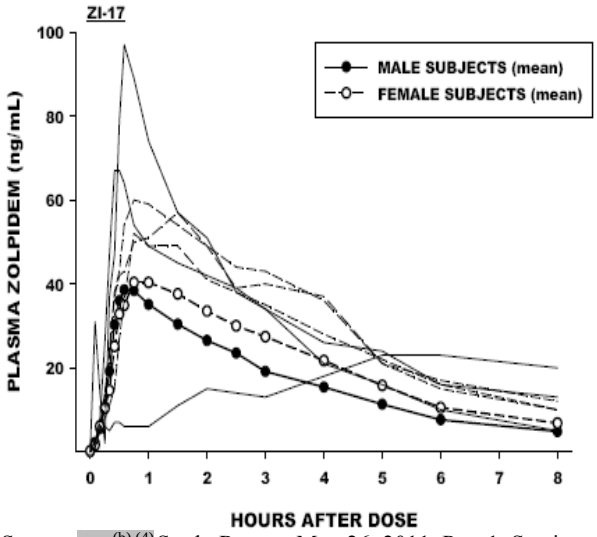
Clinical Review Conclusions on PK data:
Addressing the gender differences, the sponsor concludes that although the pharmaco-kinetics of zolpidem, C_{max}, C_4, and AUC, are higher in women, the differences are partly explained by body weight, and when weight-normalized, the differences were smaller, and not generally significant. Analysis of the gender differences by body-weight and BMI (i.e., for higher systemic exposure) did not indicate a direct relationship that could account for the size of the differences. Although a few of the subjects with high residual

plasma levels were small females, other females in the group were significantly above the study mean (combined for males and females) for both weight and BMI. When comparing the females in the 10th percentile by weight to the mean body weight for females in each study, only 63.2% weighed less than the mean weight for their study, not a sizable difference, and several females in the 10th percentile by weight in each trial weighed more than the mean weight for the males. The only generalization that could be made is that the one individual with the highest C_4 level for each trial was a smaller-size female.

Fig. 10 represents the mean zolpidem plasma concentration level for 5 studies by gender, with inclusion of individual 10th percentile levels. Mean plasma concentration levels for females are higher throughout, including at the hour 4 post-dosing in 4 of the 5 studies. Of special interest are the levels for the individual10th percentile subjects, most of whom evidenced elevated levels even at hour 8, the end of testing.

Fig.10. Mean PK profile by gender and individual 10th percentile subjects – 5 studies.





Source: (b) (4) Study Report, May 26, 2011, Part 1, Section

In the PK-endpoint trials, the zolpidem mean C_{max} levels for females ranged from 9.0% to 60.1% higher than the levels for males, and the C_4 for females ranged from 4.9% to 76.0% higher than the males.

The maximum zolpidem C_4 level for 1 or more individual females, in more than half of the trials, was higher than the mean C_{max} of the male population. The conclusion of the clinical review is that adjusting by body weight doesn't alleviate the concern that many females do have higher plasma concentration levels at the 4 hour post-dosing time point. So, the amount "on-board" for some females at 4 hours would be equivalent to the amount expected to have sedative properties shortly after dosing for the average patient.

Table 18 summarizes the number of subjects above the threshold zolpidem plasma concentration levels of 30, 40, 50, and 60 ng/mL at 4, and 5 hours post-dosing (C_4 and C_5) for males and females.

Table 18. Zolpidem plasma conc. (C4 & C5) by study #, gender, and time thresholds.

Study # Study total gender	**C4 >30 ng/mL**				**C4 >40 ng/mL**				**C4 >50 ng/mL**				**C4 >60 ng/mL**			
	4 hours		5 hours		4 hours		5 hours		4 hours		5 hours		4 hours		5 hours	
PK Trials	M	F	M	F	M F		M	F	M	F	M	F	M	F	M	F
ZI-13 Total = 32 (M13, F23)	4	17	1	8	0	10	0	0	0	2	0	0	0	1	0	0
ZI-14 Total = 24 (M15, F9)	5	2	4	1	2	1	1	1	0	1	0	1	0	0	0	0
ZI-15 Total = 33 (M19, F14)																
Fasted	2	10	1	2	1	2	0	0	0	1	0	0	0	0	0	0
Fed	3	5	3	4	1	0	1	0	0	0	0	0	0	0	0	0
PK/PD Trials																
ZI-05-009 Total = 24 (M13, F11)	2	6	1	3	0	2	0	1	0	0	0	0	0	0	0	0
ZI-16 Total = 29 (M10, F19)	1	12	0	10	0	9	0	7	0	6	0	5	0	3	0	1
ZI-17 Total = 35 (M26, F9)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	14	47	7	24	3	24	1	9	0	10	0	6	0	4	0	1

Source: Clin. Review chart, Davis

The possibility is that females, in general, may be more sensitive to this class of medications, perhaps due to metabolic differences such as the role of CYP enzymes in clearance, or other factors. The fact remains that for some females or males, higher residual plasma concentrations remain after awakening at 4 hours. A total of 176 subjects completed the 6 trials. Of the total population for the trials, 4 (4.5%) had zolpidem plasma concentrations >50 ng/mL at 4 hours post-dosing. Even looking at the zolpidem plasma concentration threshold of $\geq$60 ng/mL (higher than the C_{max} for any of the trials), at 4 hours post-dosing, 4 females (2.3% of the total studies population) exceeded that threshold.

Review of other demographic variables did not reveal any direct, or even very suggestive, relationship to zolpidem C_4 elevation.

Sponsor Conclusions on PK/PD data:
Pharmacodynamic effects of zolpidem, measured by impairment of DSST performance, were of short duration, and had returned to baseline within 3 to 4 hours after dosing. In one of the 3 studies, women had greater sensitivity to DSST impairment than men, partly explained by higher plasma concentrations, but effects nonetheless were absent 4-hours

post-dosage. In two other studies, male and female groups had comparable pharmacodynamic response.

Based on the top 10th percentile of observed distributions, individual subjects with the highest systemic exposure and/or the greatest DSST impairment were identified. Those with highest systemic exposure were predominantly women; however, men and women were equally represented among high responders. There was no coincidence between the high exposure and high response groups, indicating that individuals with higher plasma concentrations are not at risk for excessive or prolonged sedative effects and the highest 10% of pharmacodynamic response could be attributed to random variation. Age, weight, and race had no evident relationship to the occurrence of high plasma levels or high pharmacodynamic response again supporting the hypothesis that the top 10th percentile pharmacodynamic responders represent one end of an expected distribution of responses.

PD responses have been culled from the Intermezzo trials to relate to the PK results. The sponsor states that, in general, PD changes, even in females, rapidly return to baseline, and are not significantly different from zero impairment at 4 hours after dosing; therefore, female gender is not associated with a risk of residual sedative effects extending beyond 4 hours. Again, the Sponsor is referring to the mean results for the trials, which "covers up" the sizable changes of some individuals on next-morning testing.

The major characteristic of the DSST and similar PD assessments is the wide variability/"noise" inherent in the results, and it would be easy to read far more significance into the results than would be sensible. As previously discussed, the type of PD measurements used in the trials for the sleep-aid medications do not assess the types of functioning that should be considered important for next-morning activities. So, although there is no evidence of a direct relationship between PK and PD levels, safety concerns are not completely alleviated.

Trial ZI-05-009 included the most extensive list of PD tests along with corresponding PK testing. The zolpidem C_4 levels of subjects 1924 and 1923 (46.6 and 49.2 ng/mL, respectively), places the two females only slightly below the mean Cmax for all males on the trial (53.2 ng/mL). According to the Sponsor, at 20 minutes, statistically significant differences confirmative of sedating effectiveness were occurring in all the PD measurements except the SCT; cited as evidence was a decrease in the DSST mean score of -12.8 points. One subject at C_4, and 2 subjects at C_5 time-points exceeded the 12.8 point decrease.

Looking at the VAS ratings of the high PK responders, 2 rated next-morning alertness as improved (higher VAS scores), and 5 of the 7 subjects on the subjects on the C_4 >30 ng/mL list, and 3 of the 5 at C_5, registered a decrease in VAS of >25 points (on a 100mm line scale for alertness).

To evaluate whether the efficacy results of the female subjects were driving the efficacy results of the trials, statistician Dr. Tristan Massie re-evaluated the Latency to Persistent Sleep (LPS) endpoints and found that for the zolpidem SL 3.5 mg dose strength, the

efficacy results for the trial were positive (at $p<0.0001$) even without inclusion of the female subjects. So, at C_{max}, sedating effects on PD assessments are expected. Plasma concentration levels equivalent to C_{max} levels, when evidenced in individuals at 4 hours post-dosing may not have quite the same PD depressing effect. But there doesn't seem to be enough evidence available to safely make that assumption.

The sponsor contends that *there were equal numbers of men and women in the top 10th percentile for PD response (DSST in all but one of the trials). There was very little overlap between the top 10th percentile with elevated residual plasma concentration levels at 4 hours, and the top 10th percentile for significantly decreased DSST responses at 4 hours. Therefore, the individuals with high PD response are not the individuals with high systemic exposure, and vice versa.*

In general, the individuals with the highest PK levels and those with the highest PD change levels are not the same individuals, but there is some overlap that is enough to keep the open the questions of the relationship. Although there is not a direct correlation between the elevated plasma levels and the change in DSST scores at 4 hours post-dosing, ZI-16 raises the most concern regarding residual elevated plasma concentration levels of zolpidem (C_4 and C_5). The levels for several of the female subjects (# 010, 005, 003, and 004) are more than double the trial mean C_{max} for males (29.1 ng/mL). The mean change in DDST score from baseline at 20 minutes for the zolpidem 3.5 mg SL group was -9.5 ($\pm$9.5) points, $p<0.0001$. The Sponsor considered that amount of change to be evidence of sedative effects. Three subjects (# 007, 016, and 003) had recorded DSST change levels higher than that level of change at 4 hours post-dosing. Subjects #003 and 016 have evidence of both "outlier" zolpidem C4 elevation and "outlier" DSST score decreases, however, some subjects with higher C4 levels did not have significant DSST changes.

5.4 Trials with only PD Data – ZI-06-010, ZI-12, ZI-18.

The sponsor submitted results from 3 other Intermezzo trials that contained PD data without PK data. These trials were reviewed for demographic variables that might have a relationship to pharmacodynamic (PD) changes for some individuals. The ZI-18 driving trial was included, along with PD results from the two Phase 3 trials, ZI-06-010, the polysomnography (PSG) trial, and ZI-12, the outpatient study.

The ZI-12 trial included only Visual Analog Scale (VAS) asking subjects to rate (on a scale of 1 – 9), via an interactive voice response system, their perceived level of alertness/sleepiness by responding to the question "How alert do you feel?" upon awakening on mornings following use of Intermezzo. The VAS is not a measurement of functional status. Since the assessment was done shortly after awakening, there would be doubts regarding the accuracy of responses. Sedative-hypnotics residual in the system may affect the perception of next-morning effects causing unreliability of the subjective data collected.

ZI-06-010 was a pivotal Phase 3 polysomnography trial evaluating both zolpidem SL 3.5 mg and 1.75 mg dose strengths. The trial included the VAS response, and DSST testing (comparing bedtime to early morning scores).

Trial ZI-06-010

In ZI-06-010, as part of the safety evaluation, measurements of residual sedation were included. A self-assessment using the Morning Visual Analog Scale (VAS) of Alertness, and the Digit Symbol Substitution Test (DSST) were done by subjects 30 minutes after the morning wake-up (4.5 hrs post-dose) in Study ZI-06-010. The differences between zolpidem SL 3.5 mg or 1.75 mg compared to placebo were virtually unchanged for either measurement.

Looking at sub-groups, Table 19 presents the demographic summary for the subjects enrolled in trial ZI-06-010. The mean DSST change was a decline of -4.1 points (compared to -1.8 and -2.9 in the 1.75 mg and placebo groups, respectively). The DSST decrease is slightly higher for males than females in the zolpidem SL 3.5 mg and placebo groups, and reversed in the zolpidem SL 1.75 mg group.

Dividing the trial subjects by age< median or age ≥ to median, there was slightly more DSST decrease in the latter group for the 3.5 mg and placebo groups, and reversed in the 1.75 mg group. The same pattern held for comparison of the body weight < or ≥ median. Mean DSST decrease in subjects ≥ median body weight was recorded in the 3.5 mg and placebo groups, and the reverse in the 1.75 mg group. Differences overall were fairly small, less than 5 points for any group (without subtraction of the placebo group change).

Table 19. DSST – demographic summary: zolpidem SL 3.5 mg - ZI-06-010

Summary of demographic variables						
	Age Mean (%CV)	**% Female**	**% White**	**Body weight Mean (%CV)**	**BMI Mean (%CV)**	**DSST change from baseline Mean (%CV)**
10th percentile (n=8)	45.0 (31.11)	63%	38%	87.3 (13.52)	30.0 (11)	-15.25 (19.21)[a]
All subjects (n=80[1])	45.9 (25.05)	70%	53%	78.6 (18.07)	27.1 (13.65)	-4.14 (148.31)
All males (n=24)	42.5 (30.12)	0%	75%	88.7 (14.77)	27.4 (9.85)	-4.42 (158.82)[b]
All females (n=56[1])	47.4 (22.57)	100%	43%	74.3 (16.82)	26.9 (15.24)	-4.02 (143.78)[b]
Age ≥ median (n=40)	55.2 (9.60)	78%	63%	77.6 (21.62)	27.1 (14.02)	-2.89 (216.96)[c]
Age < median (n=40)	36.7 (22.34)	63%	43%	79.6 (14.42)	27.1 (14.02)	-5.39 (107.79)[c]
BW ≥ median (n=40)	46.0 (24.78)	55%	43%	90.2 (9.53)	29.7 (8.75)	-4.93 (138.95)[d]
BW < median (n=40)	45.9 (25.71)	85%	63%	67.0 (11.64)	24.4 (10.66)	-3.35 (158.21)[d]

[a]Active vs. placebo t-test p=0.90, MWUT p=0.46; [b]Male vs. female p=0.81, MWUT p=0.59
[c]Above median age vs. below median age t-test p=0.07, MWUT p=0.08; [d]Above median body weight below median body weight t-test p=0.25, MWUT p=0.29

Source: Source (b) (4) Study Report, May 26, 2011, Part 1, p.13

Tables 20 and 21 list the Sponsor designated "outliers" for DSST change. The mean change in DSST for the "outliers" is -15.3, -9.5, and -15.7 points for the 3.5 mg, 1.75 mg, and placebo groups, respectively. Comparison of the "outlier" charts for the subjects on study drug, compared to the ratings on placebo indicates some of the variability inherent in the PD measurements, even though there is no overlap of subjects.

Table 20. Top 10th percentile of DSST change: zolpidem SL 3.5 mg– ZI-06-010.

10th percentile of DSST distribution Study ZI-06-010 (PSG study) sublingual zolpidem 3.5 mg						
Subject	**Age**	**Sex**	**Race**	**Body wt**	**BMI**	**DSST change from baseline**
217	60	f	Black	88.5	32.4	-19.5
229	43	m	Black	90.7	29.5	-18.5
308	43	f	Black	93.4	33.3	-17.5
330	19	m	White	95.9	32.1	-15
327	36	m	Black	89.8	31	-14
523	42	f	White	64.5	22.9	-13.5
526	61	f	White	100.5	31.7	-12.5
301	56	f	Black	74.8	29.2	-11.5

Source: Source: (b) (4) Study Report, May 26, 2011, Part 2, Section, p.15

Table 21. Top 10th percentile of DSST change: Placebo – ZI-06-010.

10th percentile of DSST distribution Study ZI-06-010 (PSG study) Placebo						
Subject	**Age**	**Sex**	**Race**	**Body wt**	**BMI**	**DSST change from baseline**
211	54	f	Black	84.1	29.9	-30.5
310	19	m	Black	66.3	23.6	-17
521	20	f	White	52.3	18.6	-15.5
215	51	f	Black	93	33.1	-13
207	60	f	Black	84.5	28.3	-12.5
330	19	m	White	95.9	32.1	-12
334	50	m	White	86.2	25.1	-12
545	43	f	Black	78.2	30.5	-12

Source: (b) (4) Study Report, May 26, 2011, Part 2, Section, p.15

The Sponsor concluded that there was no correlation between next-day effect and gender, age or body weight in males and females on the DSST or VAS analyses.

This review reached similar conclusions as those of the Sponsor. Females composed 70% of the trial population, and 5 of 8 (62.5%) of the DSST change "outliers" in both the zolpidem SL 3.5 mg and the placebo groups, so there was no significant difference in next-day changes on the DSST test by gender analysis. The other comparisons of interest, by body weight (by gender), age, and race/ethnic group similarly indicate no significant differences between the zolpidem 3.5 mg and placebo groups when evaluating DSST change. DSST changes do not appear to have an explanation in demographic data differences.

Evaluation of VAS change from baseline (i.e., shifts on the 100 mm scale) reported an average change of -1.7, -1.8, and -3.9 for the zolpidem SL 3.5 mg, 1.75 mg, and placebo

groups, respectively. For the VAS "outliers", the changes were -40.7, -38.9 and -36.1 for the zolpidem SL 3.5 mg, 1.75 mg, and placebo groups, respectively. Again, comparisons of interest, by body weight (by gender), age, and race/ethnic group indicate no significant differences between the treatment arms.

Trial ZI-12

Trial ZI-12 was the Phase 3 out-patient trial evaluating only the zolpidem SL 3.5 dose strength compared to placebo. The trial included a response to the VAS to the interactive voice system, and data was collected for the mornings following use of Intermezzo.

Females accounted for 71% of the 150 subjects enrolled in the trial, and females were 73% of the VAS top 10^{th} percentile "outliers" for VAS change (%CV). However, the differences in VAS scores were remarkably small. The mean VAS score was 0.77 for the zolpidem SL 3.5 mg group, and 0.46 for the placebo group. The mean change in VAS scores for the "outliers" was -0.67, and -1.16 for the zolpidem SL 3.5 mg and placebo groups, respectively. The range for the "outliers" did not exceed 2.0. With such small differences, analysis by demographic groups would not yield meaningful results.

ZI-18 Driving Performance Evaluated by Demographic Data

The Sponsor's analyses of PD results by demographic variables for individual subjects were submitted only as plots and graphs rather than data sets. The sponsor's focus is on the active drug treatment drivers in the top 10% for the largest degree of driving sway change, compared to their driving on placebo. The sponsor's evaluations include:

1. Male versus female subjects
2. Subjects above the median age versus patients below the median age
3. Subjects above the median body weight versus patients above the median body weight.

The driving study ZI-18 is the only PD assessment of early morning functioning that could be considered truly informative. Unfortunately, there is not PK information for any direct correlation of plasma concentrations to driving performance. The driving study has been previously discussed for the overall study results in Section 4.3. The results of that review will not be repeated here; the focus is only on whether demographic variables could be identified that might assist in the recognition of individuals or groups more sensitive to next-morning functional changes after use of Intermezzo.

Forty subjects, were enrolled, 20 males (mean age 40.3 years), and 20 females mean age 34.3 years); the age range for all the subjects was 21-64 years. All subjects were white, except one listed other (non-black or Asian), so comparison of results by race or ethnic groups is meaningless.

Table 22. Study ZI-18 (driving study) zolpidem SL 3.5 mg, 4 hours post-dose: Demographic summary.

Summary of demographic variables							
	Age Mean (%CV)	% Female	% White	Body weight Mean (%CV)	BMI Mean (%CV)	SDLP Mean (%CV)	SDLP Δ from placebo Mean (%CV)
10th percentile (n=4)	30.8 (29.87)	25%	100%	75.0 (20.13)	24.1 (9.96)	20.2 (24.26)	4.1 (39.02)
All subjects (n=40)	37.3 (39.68)	50%	98%	72 (15)	23.2 (10.34)	16.71 (13.41)	0.83 (13.41)
All males (n=24)	40.3 (40.94)	0%	95%	79.2 (10.10)	23.9 (9.62)	16.90 (20.53)	0.73 (290.41)[a]
All females (n=56)	34.3 (37.03)	100%	100%	64.9 (12.90)	22.4 (10.71)	16.51 (19.87)	0.93 (119.36)[a]
Age ≥ median yr (n=20)	49.2 (4.06)	40%	100%	74.9 (14 .95)	23.9 (9.62)	17.12 (21.44)	0.59 (250.85)[b]
Age < median yr (n=20)	25.4 (12.99)	60%	95%	69.2 (14.45)	22.4 (10.27)	16.29 (18.48)	1.07 (173.83)[b]
BW ≥ median kg (n=21)	38.5 (40.52)	24%	95%	80.2 (8.48)	24.6 (7.72)	17.91 (21.66)	0.84 (250.00)[c]
BW< median kg (n=19)	35.9 (39.55)	79%	100%	62.9 (9.70)	21.5 (8.37)	16.86 (19.63)	0.81 (133.33)[c]

[a]Male vs. female t-test p=0.72, MWUT p=0.41
[b]Above median age vs. below median age t-test p=0.37, MWUT p=0.32; [c]Above median body weight below median body weight t-test p=0.96, MWUT p=0.97

Source: (b) (4) Study Report, May 26, 2011, Part 2, Section 4.2, p. 34

Table 23 presents the individuals in the 10th percentile in SDLP distribution at the 4 hour driving assessment.

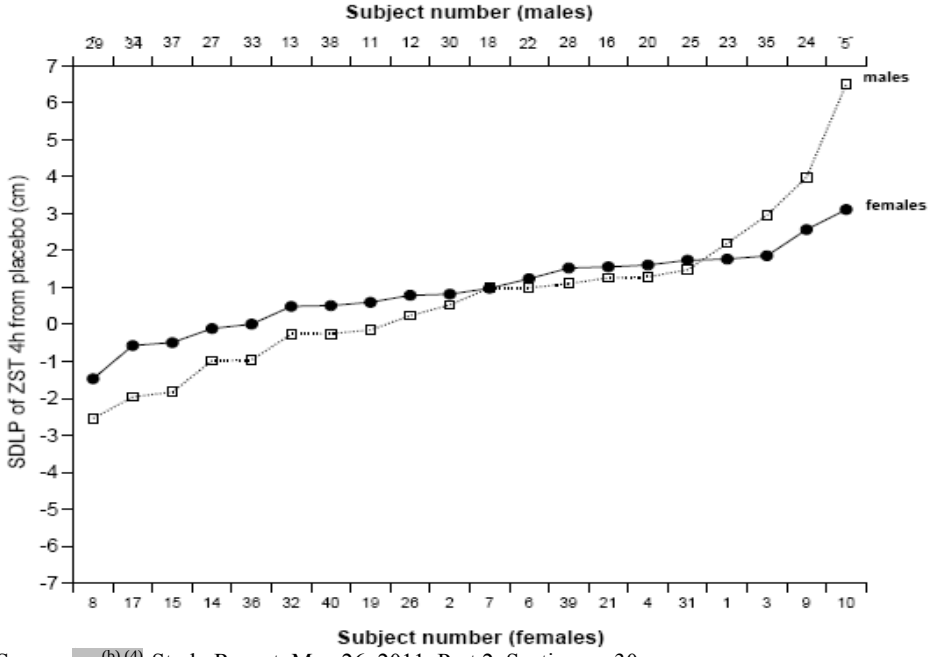
Table 23. Individuals in the 10th percentile in SDLP distribution, 4 hours – ZI-18.

Subject	Age (yrs)	Sex	Race	Body wt (kg)	BMI (kg/m^2)	SDLP (cm)	SDLP Δ from placebo (cm)
25	23	m	White	77	23.2	18.22	6.5
35	36	m	White	85	25.1	26.16	3.99
10	23	f	White	53	21.2	21.7	3.11
22	41	m	White	85	26.8	14.6	2.96

Source: (b) (4) Study Report, May 26, 2011, Part 2, Section 4.2, p. 34

Figures 11 and 12 visually represent the SDLP differences (zolpidem-placebo) at 4 hours and 3 hours post-dose, respectively. Individual male and female subjects are ranked by order of SDLP difference size (smallest to largest). In general, at 4 hours, female drivers had less SDLP change from placebo in either direction. The 3 hour driving results are more variable, but most variation is by individuals rather than by gender, although both drivers with >6.0 cm change are females.

Fig. 11. Male vs. female plots of driving performance (SDLP), zolpidem SL 3.5 mg 4 hours post-dose - Study ZI-18.



Source: (b) (4) Study Report, May 26, 2011, Part 2, Section, p. 30

Table 24. Study ZI-18 (driving study) zolpidem SL 3.5 mg, 3 hours post-dose: Demographic summary.

Summary of demographic variables							
	Age Mean (%CV)	**% Female**	**% White**	**Body weight Mean (%CV)**	**BMI Mean (%CV)**	**SDLP Mean (%CV)**	**SDLP Δ from placebo Mean (%CV)**
10th percentile (n=4)	34.0 (53.53)	50%	100%	68.0 (15.29)	23.3 (6.87)	22.22 (10.85)	5.46 (20.51)
All subjects (n=40)	37.3 (39.68)	50%	98%	72 (15)	23.2 (10.34)	17.41 (20.74)	1.46 (143.84)
All males (n=24)	40.3 (40.94)	0%	95%	79.2 (10.1)	23.9 (9.62)	17.59 (23.08)	1.21 (154.55)[a]
All females (n=56)	34.3 (37.03)	100%	100%	64.9 (12.90)	22.4 (10.71)	17.23 (18.57)	1.70 (137.65)[a]
Age ≥ median (n=20)	49.2 (4.06)	40%	100%	74.9 (14.95)	23.9 (9.62)	17.44 (23.28)	0.99 (156.57)[b]
Age < median (n=20)	25.4 (12.99)	60%	95%	69.2 (14.45)	22.4 (10.27)	17.38 (18.47)	1.92 (129.69)[b]
BW ≥ median (n=21)	38.5 (40.52)	24%	95%	80.2 (8.48)	24.6 (7.72)	17.91 (21.66)	1.43 (126.57)[c]
BW< median (n=19)	35.9 (39.55)	79%	100%	62.9 (9.70)	21.5 (8.37)	16.86 (19.63)	1.48 (60.66)[c]

[a]Male vs. female t-test p=0.47, MWUT p=0.54
[b]Above median age vs. below median age t-test p=0.17, MWUT p=0.15; [c]Above median body weight below median body weight t-test p=0.94, MWUT p=0.85

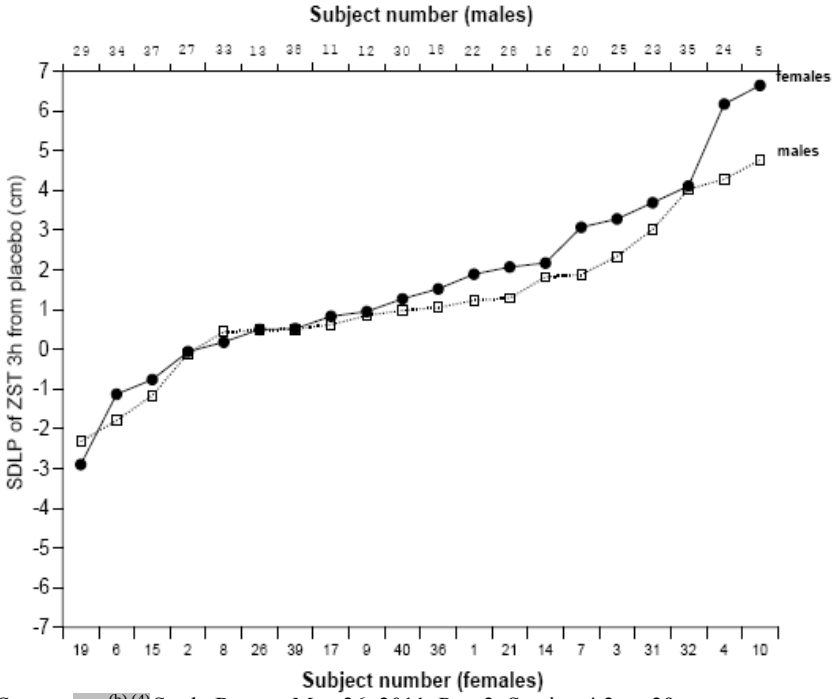
Source (b) (4) Study Report, May 26, 2011, Part 1, Section 4.2, p. 32

Table 25. Individuals in the 10th percentile in SDLP distribution – ZI-18.

Subject	**Age (yrs)**	**Sex**	**Race**	**Body wt (kg)**	**BMI (kg/m^2)**	**SDLP (cm)**	**SDLP Δ from placebo (cm)**
10	23	f	White	53	21.2	25.23	6.64
4	23	f	White	69	25	19.43	6.17
5	61	m	White	75	22.9	22.65	4.76
24	29	m	White	75	23.9	21.55	4.28

Source: (b) (4) Study Report, May 26, 2011, Part 1, Section 4.2, p. 32

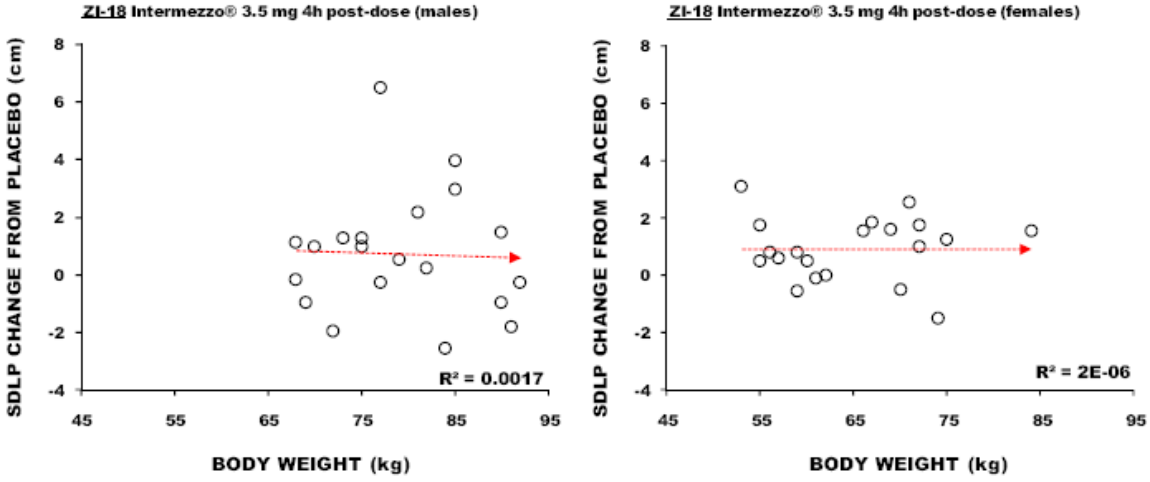
Fig. 12. Zolpidem SL 3.5 mg 3 hours post-dose - Study ZI-18



Source: (b) (4) Study Report, May 26, 2011, Part 2, Section 4.2, p. 29

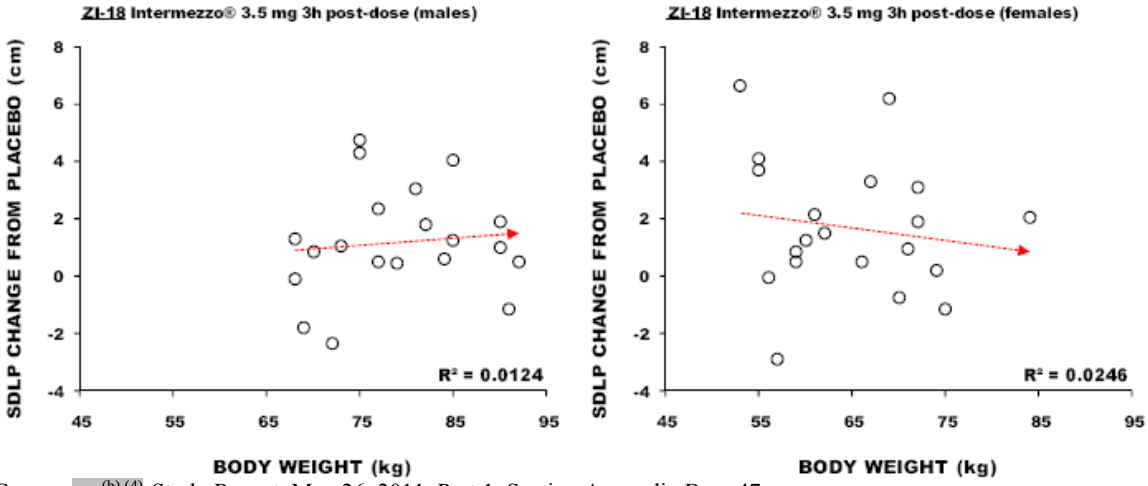
Figures 13 and 14 visually present the regression analysis of body weight data for the SDLP by gender, at 4 hours and 3 hours, respectively. Although not reaching statistical significance, there does appear to be a trend in the 3 hour driving data for the small body weight women to have an increased SDLP change.

Fig. 13. Study ZI-18 regression analysis 4 hour-SDLP, zolpidem 3.5 mg – gender by body weight



Source: (b) (4) Study Report, May 26, 2011, Part 1, Section Appendix B, p. 49

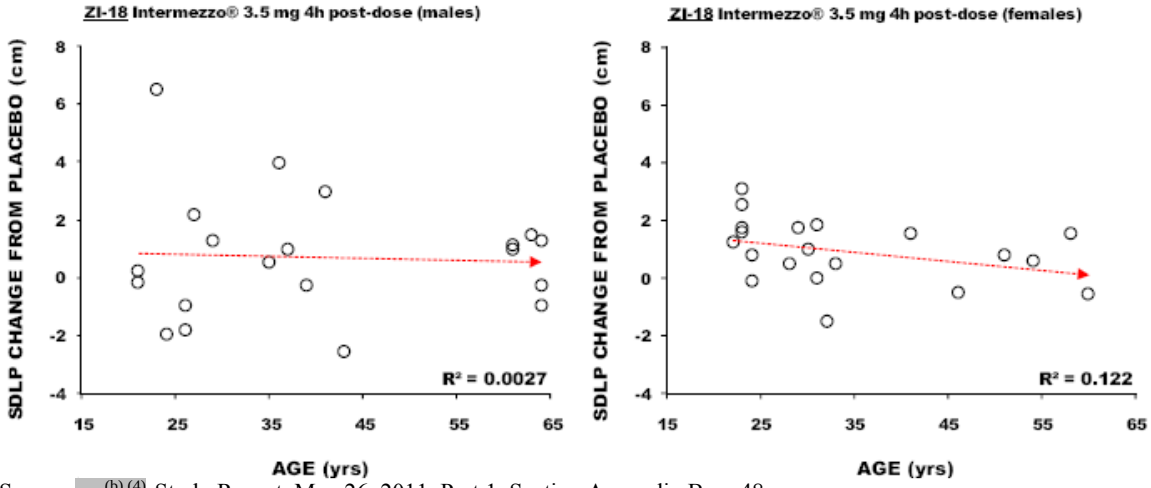
Fig. 14. Study ZI-18 regression analysis 3 hour-SDLP, zolpidem 3.5 mg – gender by body weight



Source: (b) (4) Study Report, May 26, 2011, Part 1, Section Appendix B, p. 47

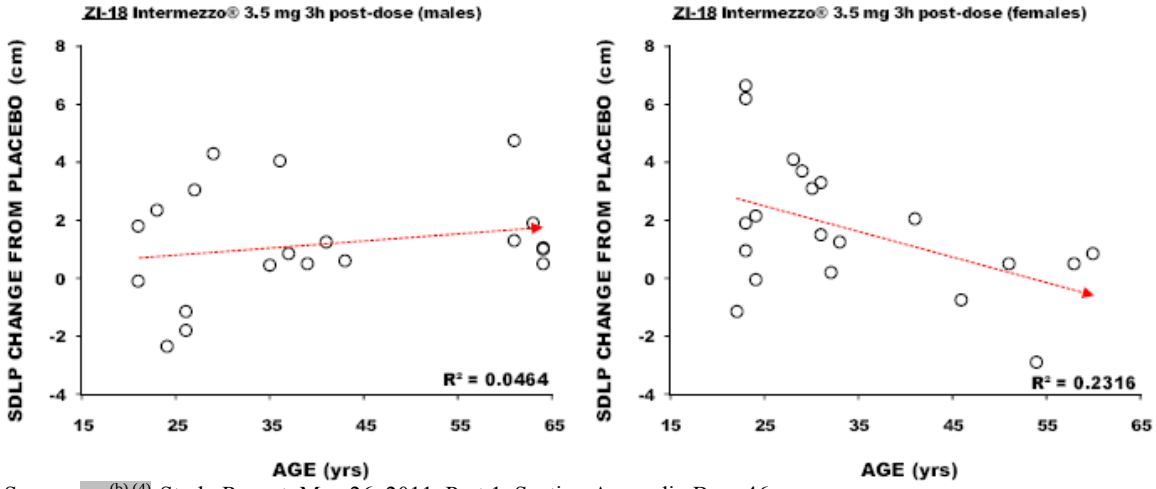
Figures 15 and 16 visually present the regression analysis of age data for the SDLP by gender, at 4 hours and 3 hours, respectively. Although not reaching significant levelsof change, there does appear to be a trend in the 3 hour driving data for younger women, and to a lesser extent, older men to have more deviation from placebo in SDLP.

Fig. 15. Study ZI-18 regression analysis 4 hour-SDLP, zolpidem 3.5 mg – gender by age



Source: (b) (4) Study Report, May 26, 2011, Part 1, Section Appendix B, p. 48

Fig. 16. Study ZI-18 regression analysis 3 hour-SDLP, zolpidem 3.5 mg – gender by age



Source: (b) (4) Study Report, May 26, 2011, Part 1, Section Appendix B, p. 46

The Sponsor concludes that *gender appears to have an effect on variability in SDLP, but not SDLP performance per se. The demographic data related to driving performance (ΔSDLP) for sublingual zolpidem 3.5 mg 3 hours after MOTN dosing and the key outcomes are as follows:*

1. Overall, the driving performance following sublingual zolpidem 3.5 mg in:

a. male subjects - not significantly different from female subjects

b. subjects above the median age - not significantly different from the subjects below the median age

c. subjects above the median body weight - not significantly different from the subjects below the median body weight

2. The demographic features of the 10th percentile group were similar to all subjects in the study.

This review reached similar conclusions for the demographic variables explored with the driving trial, mainly that the demographic characteristics of the "impaired drivers" did not differ in any significant aspect from the characteristics of the group in general. There was no significant correlation between next-day effect and age or body weight in males and females.

Conclusions for the PD Trials – ZI-06-010, ZI-12, ZI-18

Sponsor Conclusions:

Analyses of data from the clinical studies in insomniacs and the driving study in healthy volunteers indicate that age, gender and body weight do not meaningfully influence next-day residual effects of sublingual zolpidem post-MOTN dose. Demographic variables such as gender and age have no effect on a variety of objective as well as subjective measures of residual effects in the morning after MOTN ingestion of sublingual zolpidem 3.5 mg. The conclusion is based on the analysis of mean effects as well as by evaluation of the top 10th percentile of the distribution.

These findings are consistent with the pharmacodynamic outcomes described in the PK/PD analysis showing that despite the higher zolpidem plasma levels observed among some women in some studies, the pharmacodynamic effects observed at early time points returned to baseline within 3 to 4 hours post-dose, in both men and women. In fact, the top 10th percentile PD analyses did not show a consistent relationship with PK or any demographic variables.

Furthermore, the findings suggest that subjects in the 10th percentile group represent one end of the expected distribution of individual variation.

Clinical Review Conclusions:
Unlike the gender differences evidenced in the PK results, men and women were equally likely to be represented among the high responders in the PD analyses. This was true of the driving trial as well as the DSST and similar PD assessments. Again the Sponsor's conclusion that the high responders represent an expected random variation, or one end of an expected distribution of responses, makes more sense from a statistical point-of-view than from a clinical perspective. Whether decreased pharmacodynamic functioning is due to increased systemic drug exposure, or whether it is due to increased drug sensitivity, the concern is the possible increase in risk that might accompany the changes.

Overall, the May 26, 2011 submissions of additional PK and PD information indicates that, demographic variables, other than gender, do not appear to have a relationship with either PD or PK levels. So, they are of little assistance in trying to determine which individuals may be at increased risk for next-morning residual effects.

The sponsor's contention is that the individuals with elevated zolpidem plasma concentrations at 4 hours post-dosing are not "outliers" but rather individuals at one end of an expected distribution. Even when seen from the perspective of an expected distribution, it is still important to localize what the top end of the distribution represents. In this case it is plasma concentration levels of zolpidem consistently shown to be maximally sedating to the average patient, who generally experiences that level within about the first 45 minutes post-dosing, followed by a fairly rapid decline.

It is also possible that Transcept might choose to pursue marketing a single-strength Intermezzo 1.75 mg tablet. As part of the review, a possible change of dosage was explored. Table 26 indicates the extrapolated C3 and C4 levels using values of Intermezzo 3.5 mg from study ZI15. An alternative would be reformulation of the Intermezzo 3.5 mg tablet to a 3.0 mg or 2.75 mg tablet strength, with PK data to provide justification for the choice. The reformulation would place the plasma concentration range for Intermezzo at or slightly below the 8 hour post-dosing PK for the Ambien 10 mg reference drug.

Table 26. Intermezzo (Zolpidem) 3.5 mg tablet from study ZI-15

Plasma Concentration (ng/mL)		3 hrs	4 hrs
Zolpidem 3.5 mg			
Mean		34.52	26.69
SD		16.45	11.72
CV %		47.65	43.91
Zolpidem 3.0 mg			
		29.59	22.88
	Assuming 50% CV	14.79	11.44
Zolpidem 2.75 mg			
		27.12	20.97
	Assuming 50% CV	13.56	10.49

Source: Clin. Review chart, Parepally

However, such alternatives for Intermezzo should be considered in the next review cycle, with additional pertinent data. With the information currently available, concerns remain that Intermezzo 3.5 mg may not be adequately safe for small but significant proportion of individuals.

6. Departmental Reviews of CR

The chemistry review, by Lyudmila Soldatova, PhD, Office of New Drug Quality Assessment, concluded that the new proposed 4-element packaging system for Intermezzo tablets is acceptable from the CMC standpoint. Packaging capabilities were demonstrated in a batch run of the 3.5 mg strength tablets, and a the Sponsor has proposed adding the first three commercial batches for both tablet strengths to the stability program at long-term and accelerated conditions. The overall Acceptable OC recommendation for drug substance and drug product facilities was received on April 29, 2011. The 24 months expiry could be granted for the commercial drug product, 1.75 mg and 3.5 mg dosage strengths.

The review regarding the abuse potential of zolpidem tartrate SL 1.75mg and 3.5 mg, was conducted by of by Dr. Stephen Sun, Controlled Substance Staff. The review noted that due to the lower dose, Intermezzo may be less appealing for intentional misuse than other formulations of zolpidem, but that not enough was yet known regarding the "sublingual" effect on the abuse profile. Recommendations were made for:

- Monitoring of selected post-marketing adverse events (with a list of specific preferred terms),
- Discussion in the quarterly periodic report numbers and trends based on "Drug Abuse, Dependence and Withdrawal" and accident related events
- Reporting of relevant data from national abuse databases
- Expand the "dosing time chart" information to those who sleep during the day.

- In labeling and educational materials:
    - Highlight all essential safeguards to reinforce the appropriate use of the once daily dosing
    - Highlight all precautions against misuse, abuse, and diversion.
    - Highlight all concerns about residual effects to mitigate safety risks associated with operation of equipment and vehicles
    - Emphasize the language of "single" daily dose; under-emphasize use of the phrase "taken as needed"
    - Highlight appropriate warnings to prevent the concomitant use of this drug with other similar hypnotic substances including those that contain zolpidem.

No new PharmTox data was requested or submitted for the Complete Response.

Clinical Pharmacology CR review was conducted by Jagan Mohan Parepally, Ph.D., and team leader Angela Men, M.D., Ph.D. See their review for additional details. Among the conclusions are the following observations:

- Analysis of zolpidem plasma concentration by gender, based on Study ZI-15, indicates that females had approximately 30-40% higher plasma concentrations when compared to males.
- No correlation was seen between body weight and clearance of zolpidem
- 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.

The statistics review for the Complete Response was conducted by Tristan Massie, Ph.D. The review discusses the multiplicity issues related to using several cutoffs for the SDLP thresholds. Since ZI-18 is a safety study, there was no multiplicity adjustment applied for the analyses involving more than one cutoff. For the primary endpoint, the number of impaired subjects was compared to the number of improved subjects, defined as those having a decrease from placebo in SDLP under drug treatment that was below - 2.5 cm. The SDLP data suggests that ZST 3 hour, i.e., taking ZST 3 hours before awakening, impaired next day driving. Although ZST 4 hour did not reach nominal significance for the primary cutoff of 2.5 cm, or several other cutoffs specified by the sponsor, there were still other cutoffs in addition to the prespecified secondary analysis of mean differences which suggested impairment for ZST 4 hour compared to placebo.

The review by Loretta Holmes, PharmD, the Division of Medication Error Prevention and Analysis (DMEPA), was completed May 25, 2011, and the proposed proprietary name, Intermezzo is deemed acceptable.

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Appendix

Appendix Table 1. Schedule of Assessments - Protocol ZI-18.

Assessment	Screening (28 Days)	Treatment Periods		End of Study[3] or Early Termination
		Evening Day 1	Morning Day 2	
Screening				
Informed Consent	X			
Demographics	X			
Medical History (Includes con med)	X			
Driving History	X			
Sleep History	X			
Body Measurements	X			
Vital Signs	X			
Physical Examination	X			
Clinical Laboratory Tests	X			X
Urine Pregnancy Screen[1]	X			X
Urine Drug Screen	X			
12-lead ECG	X			
Practice Session Activities				
Overnight stay	X			
Practice sublingual dosing	X			
Practice Drive	X			
Treatment period				
Vital Signs		X		
Urine Pregnancy Screen[1]		X		
Urine Drug Screen		X		
Breathalyzer		X		
Bedtime Study Drug Dose		X		
MOTN Study Drug Dose			X	
Randomization		X[2]		
Adverse Events Query		X	X	
Concomitant medications		X		
Highway Driving Test			X	

1For female subjects only, if they are of childbearing potential
2Randomization occurred just prior to the first treatment period
3End of study procedures occurred after the last driving test and before subjects were driven home.
Source: Study Report – ZI-18, Section 9.5.2, p. 39

Appendix Table 2. Levels of Threshold in Relation to Impaired Driving Performance and P-values - (ZST 3h)

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZST 3h	1.75	16	21	3	0.400	0.075	8.89	0.0044
	2	13	25	2	0.325	0.050	8.07	0.0074
	2.25	11	27	2	0.275	0.050	6.23	0.0225
	2.5	10	29	1	0.250	0.025	7.36	0.0117
	2.75	10	29	1	0.250	0.025	7.36	0.0117
	3	10	30	0	0.250	<.001	10.0	0.0020
	3.25	8	32	0	0.200	<.001	8.00	0.0078
	3.5	7	33	0	0.175	<.001	7.00	0.0156
	3.75	6	34	0	0.150	<.001	6.00	0.0313
	4	6	34	0	0.150	<.001	6.00	0.0313
	4.25	4	36	0	0.100	<.001	4.00	0.1250
	4.5	3	37	0	0.075	<.001	3.00	0.2500
	4.75	3	37	0	0.075	<.001	3.00	0.2500
	5	2	38	0	0.050	<.001	2.00	0.5000
	5.25	2	38	0	0.050	<.001	2.00	0.5000
	5.5	2	38	0	0.050	<.001	2.00	0.5000
	5.75	2	38	0	0.050	<.001	2.00	0.5000
	6	2	38	0	0.050	<.001	2.00	0.5000
	6.25	1	39	0	0.025	<.001	1.00	1.0000
	6.5	1	39	0	0.025	<.001	1.00	1.0000

Source: Study Report – ZI-18, based on Table 14.2.1-2, p. 56

Appendix Table 3. Levels of Threshold in Relation to Impaired Driving Performance and P-values - ZOP)

Treatment Versus Placebo	Number of Subjects				Probability		McNemar Statistic	p-value
	Threshold (cm)	Impaired	Neutral	Improved	Impaired	Improved		
ZOP	1.75	22	18	0	0.550	<.001	22.0	<.0001
	2	19	21	0	0.475	<.001	19.0	<.0001
	2.25	19	21	0	0.475	<.001	19.0	<.0001
	2.5	18	22	0	0.450	<.001	18.0	<.0001
	2.75	17	23	0	0.425	<.001	17.0	<.0001
	3	16	24	0	0.400	<.001	16.0	<.0001
	3.25	16	24	0	0.400	<.001	16.0	<.0001
	3.5	14	26	0	0.350	<.001	14.0	0.0001
	3.75	13	27	0	0.325	<.001	13.0	0.0002
	4	13	27	0	0.325	<.001	13.0	0.0002
	4.25	11	29	0	0.275	<.001	11.0	0.0010
	4.5	10	30	0	0.250	<.001	10.0	0.0020
	4.75	9	31	0	0.225	<.001	9.00	0.0039
	5	9	31	0	0.225	<.001	9.00	0.0039
	5.25	8	32	0	0.200	<.001	8.00	0.0078
	5.5	6	34	0	0.150	<.001	6.00	0.0313
	5.75	5	35	0	0.125	<.001	5.00	0.0625
	6	4	36	0	0.100	<.001	4.00	0.1250
	6.25	4	36	0	0.100	<.001	4.00	0.1250
	6.5	4	36	0	0.100	<.001	4.00	0.1250

Source: Study Report – ZI-18, based on Table 14.2.1-2, p. 59

Appendix Table 4. SDLP (cm) for ZST 4h and placebo groups, and difference for ZST 4h

Subject ID	ZST 4h SDLP (cm)	Placebo SDLP (cm)	Difference from placebo (cm)
1 F 26	22.1	20.24	1.77
2 F 24	14.14	13.32	0.82
3 F 31	14.69	12.83	1.86
4 F 23	14.87	13.26	1.62
5 M 61	18.86	17.87	0.99
6 F 22	18.40	17.16	1.24
7 F 30	17.31	16.33	0.98
8 F 32	15.41	13.94	-1.47
9 F 23	19.03*	16.46	2.57
10 F 23	21.70*	18.59	3.11
11 M 43	17.32***	19.86	-2.54
12 M 37	13.03	12.04	0.99
13 M 64	18.24	18.50	-0.26
14 F 24	12.12	12.23	-0.11
15 F 46	18.54	19.03	-0.49
16 M 21	13.66	13.42	0.24
17 F 60	12.92	13.51	-0.57
18 M 64	16.66	15.37	1.29
19 F 54	17.25	16.65	0.60
20 M 63	21.43	19.95	1.48
21 F 21	18.75	17.19	1.56
22 M 41	14.60*	11.64	2.96
23 M 27	17.87	15.67	2.20
24 M 29	18.53	17.27	1.26
25 M 23	18.22**	11.72	6.50
26 F 51	21.92	21.13	0.79
27 M 21	14.91	15.05	-0.15
28 M 61	19.33	18.22	1.11
29 M 24	17.97	19.93	-1.96
30 M 64	15.41	16.39	-0.98
31 M 29	13.64	11.90	1.74
32 F 28	10.31	9.82	0.49
33 M 35	9.23	8.70	0.53
34 M 26	15.52	16.48	-0.96
35 M 36	26.16**	22.17	3.99
36 F 31	16.67	16.66	0.01
37 M 26	14.28	16.11	-1.83
38 M 39	16.80	17.05	-0.25
39 F 58	15.73	14.20	1.53
40 F 33	16.31	15.80	0.51

* = impaired at 2.5 cm threshold
** - impaired at 3.5 cm threshold
*** = improved at 2.5 cm threshold
Source: Clin. Review, Davis

Appendix Table 5: Description of the Digit Symbol Substitution Test, Symbol Copying Test, Visual Analog Scale and Buschke Memory Recall Test (simplified)

The Digit Symbol Substitution Test (DSST) is one of the tests of the Wechsler Adult Intelligence Scale (Matarazzo, 1972). It is one of many behavioral measures that vary with differing states of alertness and/or sedation. It is aversely affected by sleep deprivation and night shift work in the absence of adequate daytime sleep. It is also used as a measure of drug-induced sedation, like following intake of alcohol or sedative-hypnotics. The DSST is interpreted to measure complex pharmacodynamic activity, short-term memory, and fine motor control. Outcome measures are number of correct substitution during a defined time period (usually 90 seconds or 3 minutes).
Patients will be given a set of symbols with corresponding single-digit numbers. The test also will contain "blank" boxes with corresponding digits. Patients will be asked to make as many symbol-for-digit substitutions as possible working from left to right without skipping any boxes within a 90-second period. The number of correct substitutions in the 90-second period will be recorded. Patients will need to be monitored while filling out the forms.

The Symbol Copying Test (SCT) is a test with identical graphomotor requirements as the DSST but without visual search, memory, or coding demands. Outcomes are considered noncoding motoric equivalent measures to the DSST. SCT is as widely used and as sensitive as the DSST including measurement of the acute and residual effects of flurazepam and triazolam. Outcome measure is number of correct symbols copied during a defined time period (usually 90 seconds or 3 minutes). Patients will be given a sheet filled with double rows: the upper row will be filled with symbols, the lower row will be empty. Patients will be asked to make as many and accurate symbol-copies as possible working from left to right without skipping any boxes within a 90-second period. The number of correct copies in the 90-second period will be recorded. Patients will be monitored while filling out the forms.

Visual Analog Scale (VAS): Patients will be asked to score the following question: "How alert do you feel right now?" On a 100 mm VAS, a score of 0 indicates "very sleepy" and a score of 100 indicates "wide awake and alert". The length of the VAS response will be recorded.

Buschke Word Recall Test is applied with many (minor) variations. Usually, a list of 10–15 words is presented at a constant rate for one or more trials over a given period of time; the number of words recalled is tested after each trial. A variation includes selective reminding only of items forgotten on a given trial. Depending on the time interval for retrieval, this test is believed to measure retrieval from short-term memory, retrieval from long-term memory, and long-term memory storage. This test is one of the most widely used tests for memory impairment or drug effects on memory (O'Connell 2002).
Outcome measure is the number of correct words recalled under defined circumstances. The patient is to recall as many words as possible in any order. A list of 15 words will be read, at a rate of one word per second, during each test session. Immediately after the reading, patients will write as many words down on paper as they remember. Patients will

be given 1 minute to recall as many words as possible. The scores of this test are the number of words properly recalled.

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

/s/

CAROLE L DAVIS
07/12/2011
CR Clinical Review

RONALD H FARKAS
07/12/2011

MEMORANDUM

DATE: October 26, 2009

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-328

SUBJECT: Action Memo for NDA 22-328, for the use of Intermezzo (zolpidem tartrate sublingual lozenge) for Middle of the Night (MOTN) awakenings

NDA 22-328, for the use of Intermezzo (zolpidem tartrate sublingual lozenge) for Middle of the Night (MOTN) awakenings, was submitted by Transcept Pharmaceuticals on 9/30/08. Zolpidem is currently marketed as a hypnotic for the treatment of insomnia characterized by difficulty falling asleep, and this application is submitted under section 505(b)(2) of the FD&C Act, with Ambien (zolpidem) as the reference product. The current application proposes the use of the sublingual lozenge on an as needed (prn) basis by patients who experience frequent middle of the night awakenings to be taken when such a patient experiences such a MOTN awakening. The sponsor proposes to indicate this product for only once a night dosing, and only when the patient has at least 4 hours of sleep left. The sponsor has performed two randomized controlled trials examining the effectiveness of Intermezzo for this use, as well as several clinical pharmacology studies, the requisite chemistry and manufacturing controls (CMC) information, and other data.

The application has been reviewed by Dr. Carole Davis, medical officer, Dr. Tristan Massie, statistician, Dr. Jagan Parepally, Office of Clinical Pharmacology, Dr. Melissa Banks, pharmacologist, Dr. Silvia Calderon, Controlled Substances Staff, Shawna Hutchins, Robin Duer, Division of Risk Management, Dr. Loretta Holmes, Division of Medication Error Prevention and Analysis, Dr. Sharon Watson, Division of Drug Marketing, Advertising, and Communications, Dr. Wendy Wilson, chemist, and Dr. Ron Farkas, Neurology Team Leader. The clinical team recommends that the application be approved. I will very briefly describe the relevant data, and offer my rationale for the division's action.

Effectiveness

As noted above, the sponsor has submitted the results of two randomized controlled trials examining the effect of zolpidem tartrate sublingual lozenge on reducing sleep latency in a single episode of MOTN awakening.

Study 010 was a 3 period polysomnographic (PSG) study in which patients were admitted to a sleep lab and awoken 4 hours after lights out. They were given Intermezzo 1.75 mg, 3.5 mg, and placebo in random order, kept awake for an

additional 30 minutes, followed by a second lights out at that point. The primary outcome measure was Latency to Persistent Sleep (LPS), measured from the time of the second lights out. Each treatment period consisted of 2 days of treatment, and there was a 5-12 day washout period between treatment periods. In this study, both doses were statistically significantly superior to placebo, and there was clear superiority of the 3.5 mg dose compared to the 1.75 mg dose. Numerous secondary outcomes were also significantly improved in both doses compared to the placebo group, including objective and subjective Total Sleep Time (TST), and subjective latency. In this study, although there were statistically significant differences seen in the number of MOTN awakenings between each dose and placebo, the numerical differences were minimal:

# of MOTN Awakenings

	Screening	Placebo	1.75 mg	3.5 mg
Mean	4.0	4.1	3.7	3.7
Median	3.5	4.0	3.0	3.5

Study 12 was a 4 week, double-blind, out-patient study in which patients were randomized to receive Intermezzo 3.5 mg or placebo. The primary outcome was (subjective) Latency to Sleep Onset (LSO), as assessed by patients' responses to the question, "How long did it take you to fall asleep after taking your study medication?". In this study, the difference between Intermezzo and placebo on the primary outcome was highly significant ($p<0.001$) at the last time point, and at early weekly timepoints as well. Subjective Wake Time After Sleep Onset (WASO) was highly significant, as was subjective # of MOTN awakenings. However, the difference between drug and placebo on subjective TST (the first secondary outcome to be assessed in the sponsor's hierarchical plan) was not significant, with a p-value of 0.13, although this may have occurred secondary to baseline differences (see Dr. Massie's review, page 31).

In this study, patients had to call a central phone number when they woke up in the middle of the night, and had to receive permission to administer the dose. Permission was granted only if the patient had at least 4 hours left to sleep.

Safety

There were no documented safety issues that would preclude approval. In particular, tests of alertness and the Digit Symbol Substitution Test (DSST) were administered in the morning in Study 010, and neither dose was different from placebo. In Study 12, sleepiness in the morning and alertness was measured on a 9 point scale, and the difference favored Intermezzo over placebo ($p=0.03$).

The sponsor performed a study in which Intermezzo 1.75 and 3.5 mg doses were compared to placebo, given during the day, on the DSST. Both dose showed decrements compared to placebo, but results in all three groups were essentially similar by 3 hours post-dose.

Dr. Farkas discusses several studies from the literature that attempt to measure the effects on driving of various doses of zolpidem.

One study, by Leufkens et al, found that driving performance (as measured by the standard deviation of lateral position [SDLP], a relatively standard measure of driving impairment) 5-6 hours after a 4 AM dose of zolpidem 10 mg was "moderately impaired". Although the effects of alcohol were not assessed in this study, the authors report that the degree of impairment (SDLP of 3.5 cm) in this study seen with zolpidem was greater than that seen with alcohol in other studies at an alcohol concentration of 0.5 mg/ml, the legal limit in many countries (SDLP of 2 cm). Another study, by Verster et al, examined the effects on SDLP 4 hours after a MOTN 10 mg dose of zolpidem. In this study, the SDLP was 3 cm after zolpidem, and 1 cm at a blood alcohol level of 0.5 mg/ml.

In neither of these studies were blood levels of zolpidem measured, but data in this application demonstrates that the zolpidem blood level is about 24 ng/ml at 6 hours after a 10 mg dose of zolpidem. Several studies performed by the sponsor document that blood levels of zolpidem 4 hours after a MOTN dose of 3.5 mg of Intermezzo are about 25 ng/mL.

COMMENTS

The sponsor has submitted the results of two randomized controlled trials that demonstrate that zolpidem 1.75 mg and 3.5 mg reduce sleep latency when taken after awakening in the middle of the night. Further, no obvious safety signals of concern were seen in this application.

Despite these findings, I believe that there are potential significant safety issues raised in this application. In particular, I am concerned about the possibility for the occurrence of medication errors with potentially serious consequences that might arise from the unique use of this product.

As noted, this product is intended to be taken by the patient in the middle of the night to help them return to sleep. It is to be taken only once each night, and only when the patient has at least 4 hours left to sleep. I believe that the unique use of this product has the potential to predispose to errors of two kinds, the possibility that the patient may take more than one dose per night (for more than one episode of MOTN awakening) and the possibility that the patient may take a dose (even if only one dose) with less than 4 hours of sleep left.

Because this drug is specifically to be taken in the middle of the night, and because this drug can induce amnesia, we have no assurance that patients will remember that they have taken their (presumed single) nightly dose, and therefore the risk of a patient taking a second (and perhaps another) dose in the same night is real. In this regard, several factors, in my view, increase this risk (beyond the fact that the patient is supposed to administer it in the middle of the night).

In addition, as the data from Study 010 demonstrates, patients successfully treated with a single lozenge still have, on average, 2-3 awakenings subsequent to the episode treated on any given night. The combination of readily available drug by the bedside and the occurrence of numerous MOTN awakenings after a treated MOTN awakening, combined with possibility of amnesia for the treated event, presents, in my view, a very real concern for multiple dosing in a given night.

This is potentially problematic, because blood levels of zolpidem after 2 doses of Intermezzo may reach very high levels in the morning, with attendant potential significant effects on, for example, driving. For example, as Dr. Farkas describes, two, 3.5 mg doses of Intermezzo taken 2 hours apart will result in a blood zolpidem levels associated with impaired driving. Levels 4 hours after a second dose that was taken less than 2 hours after a previous dose would result in levels even higher.

In addition, subjects were given a 2 week supply of drug at each time point in Study 12. A total of 15% (22/150) of zolpidem patients and 8% (12/145) of placebo patients returned at least 4 fewer lozenges than they should have at each visit. This at least raises the possibility that the "missing" lozenges were actually taken by the patient; that is, it is reasonable to presume that patients administered more than one dose on some nights.

Further, we have little assurance that patients will reliably take their dose with at least 4 hours of sleep time left.

The only study that examined this possibility was, of course, Study 12. However, this study ***required*** patients to call a central number and receive permission to

take the dose, and this permission was granted only if the patient had at least 4 hours of sleep time left. Clearly, the conditions of this study cannot be used to predict how reliably patients will dose themselves if the drug were marketed.

Nonetheless, despite the constraints of this protocol, evidence suggests that some patients did, in fact, take drug with less than 4 hours left to sleep.

Specifically, a total of 3.3% (N=5) of zolpidem patients and 1.4% (N=2) of placebo patients actually reported taking a dose with less than 4 hours of sleep time left, most after having called and having been told not to take the dose. Further, a total of about 2% of patients reported (based on AM phone calls) having arisen and being out of bed less than 4 hours after dosing.

This is of particular concern, given that plasma levels of zolpidem 4 hours after a 3.5 mg dose of Intermezzo are already in the range associated with impaired driving (see above). Clearly, a similar dose taken with fewer than 4 hours left to sleep will result in significantly higher plasma levels upon awakening.

These issues have been discussed in numerous meetings with members of the review team (including with members of DMEPA) and the sponsor. The sponsor has attempted to address our concerns in numerous ways.

Regarding the possibility that patients may be amnestic after administering a 3.5 mg dose of Intermezzo, the sponsor cites an article suggesting that such a dose would not cause amnesia. However, memory impairment was seen in a study comparing several doses of Intermezzo and placebo in healthy volunteers. The sponsor further asserts that memory impairment was maximal at 20 minutes, when most patients would be asleep. However, a substantial number of patients were awake at 20 minutes in Study 12, and it is certainly possible that memory impairment could last significantly beyond 20 minutes (the study in which this finding was seen was not adequately designed to reliably detect effects over extended periods of time). Further, in this study, drug was given at 8 AM, and could not assess the effects on memory in a patient who awoke in the middle of the night.

The sponsor also notes that patients with insomnia are “hyper-aroused”, and less likely to experience amnesia related to being sleepy. However, the assertion that this “hyper-arousal” would mitigate any potential drug-induced memory impairments in a patient who is sleepy is unsupported.

They also assert that events that occur within 5 minutes of falling asleep are remembered less well than those events that occur out further in time in relation to falling asleep, and that only about 1% of doses were associated with sleep onset of 5 minutes or less. Nonetheless, this provides, in my view, little reassurance that patients who take longer than 5 minutes to fall asleep will reliably recall that they have taken a dose previously.

The sponsor has made several proposals that they believe will adequately mitigate the risks described. They have proposed a REMS consisting of a Medication Guide and a Phase 4 study to evaluate any adverse events of the sort discussed. These approaches have been discussed with the review team, and we consider these measures likely to be inadequate to prevent such errors (indeed, some of the proposals, [e.g., Phase 4 studies and pharmacovigilance measures] can only document problems that may have occurred, and are obviously not designed to prevent any errors).

For these reasons, then, I do not believe the sponsor has documented that this drug can reliably be used safely. These issues have been discussed at numerous internal meetings, many of which occurred after Drs. Davis and Farkas filed their reviews recommending approval. I believe it is accurate to state that, after these meetings and discussions, they both agree with this conclusion.

To address our concerns, the sponsor might perform driving tests under some of the more extreme conditions that might result from errors (for example, they might document that there is no important effect on driving if a dose of Intermezzo is taken 2 hours or so before awakening), or that there is no important effect on driving if multiple doses are taken at various times. In my view, alternative packaging that would prevent multiple dosing during the night, and/or that might even prevent dosing with less than 4 hours of sleep left, might be developed. I believe it would be useful for the sponsor to pursue this approach, assuming such packaging is available or could be developed.

For the reasons discussed, I will issue the attached Complete Response letter.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
10/28/2009

Cross-Discipline Team Leader Review

Date	8/11/2009
From	Ronald Farkas MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-328
Applicant	Transcept
Date of Submission	9/30/2008
PDUFA Goal Date	7/30/2009
Proprietary Name / Established (USAN) names	Intermezzo
Dosage forms / Strength	Sublingual tablet, 1.75 mg / 3.5 mg
Proposed Indication(s)	Insomnia following middle-of-the-night awakening
Recommended:	*Approval*

1. Introduction

Zolpidem tartarate sublingual lozenge is being developed under section 505(b)(2) by Transcept for the as-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN). To support the application, the sponsor is referencing safety and efficacy information FDA relied on for approval of Ambien® (NDA 19-908).

Studies for this NDA were conducted under IND 69,209.

2. Background

Zolpidem tartrate is a non-benzodiazepine sedative-hypnotic approved in the U.S. as Ambien tablets in 1992 for the treatment of short term insomnia characterized by difficulties with sleep initiation. Ambien labeling indicates that patients should have at least 7 to 8 hours of time remaining in bed after dosing in order to avoid residual sedative effects the following morning.

The sponsor developed sublingual zolpidem *not* for sleep initiation at bedtime, but instead for the as-needed treatment of difficulty returning to sleep after MOTN awakening. Difficulty returning to sleep after MOTN awakening is a common complaint of insomniacs.

The sponsor notes that many patients with MOTN insomnia do not experience MOTN awakenings every night and do not have difficulty falling asleep at bedtime, but may dose themselves prophylactically with hypnotics each evening before bedtime because they cannot predict when such awakenings may occur. In contrast since Intermezzo is intended for use

only when patients have difficulty falling back to sleep after MOTN awakening, the sponsor proposes that the use of Intermezzo may reduce overall patient exposure to hypnotic drugs by reducing both dose and frequency of use.

No other sedative-hypnotic or zolpidem product is currently approved in the U.S. for as-needed treatment of MOTN awakenings.

The sponsor notes that a zolpidem-containing drug for MOTN dosing should be formulated to deliver the drug such that the threshold concentration for sedation is achieved rapidly, and so that the blood/tissue concentrations after final awakening do not result in residual effects (the sponsor limits dosing to within no less than 4 hours of expected final awakening). The sponsor developed a sublingual dosage form of zolpidem that they assert is absorbed rapidly through the oral mucosa of the sublingual cavity. The sponsor studied 3.5 mg zolpidem for adults and 1.75 mg zolpidem for elderly, lower doses than used in Ambien, in an attempt to decrease residual effects at awakening. The recommended dose of Ambien is 10 mg for adults <65 years old, and 5 mg for adults >65 years old.

Two pivotal studies were conducted in a total of 377 patients with a history of insomnia characterized by difficulty returning to sleep after MOTN awakening. Study ZI-06-010 was an objective sleep laboratory study, and study ZI-12 was a subjective outpatient study. The two pivotal studies included patients 18-64 years old, but no geriatric patients. Instead, FDA agreed that it would be adequate for the sponsor to base dosing in the elderly on a pharmacokinetic study only, as noted in meeting minutes of 09 February 2006.

During review of the NDA, the Division expressed concern to the sponsor about potential medication dosing errors that might be associated with use of Intermezzo due to MOTN dosing, including inadvertently taking more than 1 pill per night, and taking a dose with less then 4 hours of sleep time remaining. The sponsor's submission in response to this concern was considered a major amendment, extending the PDUFA data by 3 months.

3. CMC/Device

Dr. Wendy Wilson conducted the CMC review, and recommended approval for both the 1.75 mg and 3.5 mg strengths of Intermezzo, pending final labeling.

The sponsor states that a bicarbonate [redacted] (b) (4)

CDTL note: As described under section 4 below, the claim [redacted] (b) (4) is not adequately supported.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Dr. Melissa Banks, who found the application approvable pending agreement on labeling recommendations.

A local toxicity study was the only nonclinical study requested. It demonstrated some potential for mild irritation and potential to aggravate pre-existing tissue injury. The local irritation showed evidence of reversibility.

Dr. Banks notes that if pediatric studies will be conducted by the sponsor, in addition a juvenile animal toxicology study(ies) will likely be required to support the clinical trial(s)due to the change in route, altered maximum recommended human dose, and administration details of Intermezzo.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Jagan Parepally, who found the submission acceptable from a Clinical Pharmacology and Biopharmaceutics point of view pending agreement of labeling recommendations in the package insert.

The following PK studies were conducted:
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. Food effect on PK profile was examined.
- 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.

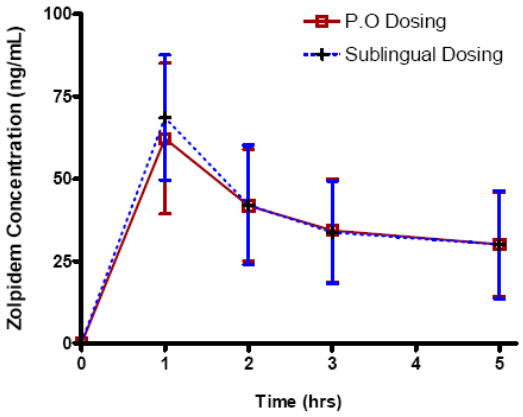
Dr. Parepally's major findings were as follows:

- The systemic exposure (AUC and Cmax) after administration of a 3.5 mg sublingual zolpidem tartrate tablet is well below the exposure to zolpidem after administration of a 10 mg oral zolpidem tartrate tablet (Ambien®) which was found to be safe. [Study ZI-15]
- 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 about 47 ng/mL. At about 6.5 hrs, plasma concentration of zolpidem would be 10% of Cmax. Zolpidem plasma concentration after 3 and 4 hrs would be about 25.6 ng/mL or 54% of Cmax and 16.1 ng/mL or 34% of Cmax respectively.
- Bioequivalence criteria were met between commercial formulation and IND formulation under fasting conditions.[Study ZI-13]

- Cmax decreased by about 38% and AUC decreased by 19% on an average, following administration of Intermezzo with food. Tmax was prolonged from 1 hour in the fasted state to 3 hours in the fed state [Study ZI-15]

CDTL: Zolpidem blood levels are similar at 4 hours in the fed versus fasted state. While the Tmax is delayed by fed state, raising concern for increased residual effects in the morning, the concomitant decrease in Cmax and AUC appears largely to counteract this risk, at least by 4 hours.

- In elderly patients, mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher compared to adults. Exposure to zolpidem from 1.75 mg and 3.5 mg sublingual zolpidem was dose proportional under fasting conditions in elderly. Reducing dosing by half in elderly therefore appeared reasonable to Dr. Parepally. [Study ZI-14]
- Rapidity of onset and route of absorption: The pharmacokinetic profiles appeared to be similar for sublingual and P.O. dosing (figure below). Dr. Parepalli concludes that PK sampling time points were inadequate to quantitate the absorption differences between sublingual and oral administration.



In a pharmacodynamic study ZI-16 with Intermezzo DSST scores were evaluated for sublingual versus P.O. (immediate swallowing) administration in comparison with placebo treatment. DSST scores was numerically more affected by P.O. dosing, although results were overall very similar to that for sublingual dosing. DSST score returned to the baseline within about 4 hrs postdose corresponding to 30 ng/mL mean plasma zolpidem concentration.

CDTL: Neither the PK nor PD data adequately support a claim (b) (4) (b) (4) would have to be supported by evidence of clinical meaningfulness to be used in labeling. In addition, such comparative claims generally require replication.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Tristan Massey was the primary statistical reviewer. Dr. Carole Davis conducted the clinical efficacy review. They both conclude that the data from the key efficacy studies, ZI-06-010 and ZI-12, support the superiority of Intermezzo over placebo for reducing sleep latency after middle of the night awakening.

PSG Study ZI-06-010

ZI-06-010 was a 3-period crossover PSG study in which patients were awakened on a scheduled basis 4 hours after initial lights out, and were not permitted to attempt to go back to sleep for 30 minutes.

CDTL: The model of MOTN awakenings used in this study appears similar enough to spontaneous MOTN awakenings to contribute to evidence of effectiveness, but the actual LPS values would not be expected to predict sleep latency in clinical use given that the MOTN awakenings were not spontaneous and patients were not permitted to go back to sleep for 30 minutes.

Patients received, in predetermined order, either Intermezzo 1.75 mg, 3.5 mg, or placebo during each 2-night treatment period. Treatment periods were separated by 5- to 12 days. The primary endpoint was LPS when returning to sleep after the scheduled MOTN 30 minute awake time, averaged over the two consecutive nights in the PSG laboratory.

To enroll, patients had to have at least 3 awakenings per week with a mean sleep onset latency (SOL) $\geq$ 30 minutes in a 10-day screening period. Patients with continued eligibility then underwent 2-night PSG screening on single-blind placebo, requiring a mean LPS $\geq$ 20 minutes after scheduled MOTN awakenings, and neither night LPS < 15 minutes to remain eligible.

Patients were analyzed who had LPS data from at least one night of one treatment period.

Primary endpoint
Drs Massey and Davis conclude that the primary endpoint was statistically positive ($p < 0.001$). Mean LPS was 37 minutes for placebo, 17 minutes for 1.75 mg, and 11 minutes for 3.5 mg. There was no compelling evidence of a treatment by period interaction or carryover effect. Data from crossover period 1 only was also statistically significant for both doses versus placebo. Imputation of unfavorable LPS similar to worse-case for missing data did not meaningfully change the results.

Baseline Imbalance:
There was some suggestion in the data that the Latency to Persistent Sleep (LPS) *pre*-MOTN awakening varied significantly with the crossover period as well as the treatment group. This

is of concern because if there were, in fact, significant differences at baseline then the differences seen after treatment might not have been attributable to the treatment, but instead might have been due to baseline differences among groups. However, Drs. Massy and Davis conclude that despite the possible group difference in LPS prior to scheduled awakening, the prespecified primary analysis, as well as most other analyses (e.g., restricted to the first day of two days in each crossover period, or restricted to a particular crossover period) seem to support a significant treatment effect on LPS after scheduled awakening, and that the balance of the data suggests robustness of the treatment effect.

CDTL: There is no clear clinical interpretation to the baseline imbalance, or suggestion that it affected the overall study outcome, and I agree with Drs. Massey and Davis that the finding appears robust despite the baseline imbalance.

Secondary endpoints
The analysis plan specified that the following secondary endpoints would be tested in the following order for the high dose, 3.5 mg arm. Drs. Massey and Davis found that the prespecified analysis for each of these secondary endpoints was significant (select p-values indicated):

1. Objective TST, $p < 0.0001$
2. Objective Sleep efficiency
   The Sleep Efficiency endpoint was highly correlated ($r = 0.999$) with TST, and does not seem to provide any distinct efficacy information.
3. Subjective sleep quality rating
4. Subjective Sleep Onset Latency (SOL), $p<0.0001$
5. Subjective TST, $p < 0.0001$

Following the above, objective LPS for low dose was tested.

1. Objective TST, $p < 0.0001$
2. Subjective sleep quality rating
3. Subjective Sleep Onset Latency (SOL), $p<0.0001$
4. Subjective TST, $p=0.0159$

There was no difference for WASO between either dose group and placebo.
CDTL: Intermezzo does not decrease the number or length of subsequent MOTN awakenings.

CDTL conclusion, PSG study: The study supports the efficacy of both the 3.5 and 1.75 mg doses of Intermezzo in adult patients.

Subjective Study ZI-12

ZI-12 was a 4-week, double-blind outpatient study of 3.5 mg Intermezzo versus placebo. The study enrolled patients with primary insomnia characterized by MOTN awakenings with difficulty returning to sleep. All endpoints were subjective. The primary efficacy endpoint

was latency to sleep onset (LSO) for spontaneous MOTN awakenings, reported in the morning by the patient in response to the question "How long did it take you to fall asleep after taking your study medication?"

Efficacy analyses were to include all subjects who took at least one dose of study drug during the double-blind treatment phase of the study and who had LSO-MOTN data from at least one night of the double-blind treatment period. The baseline value for key efficacy measures was the mean for nights during which the subject took single-blind placebo during a two-week screening run-in period. If a patient didn't fall asleep after MOTN awakening, LSO was set to 4 hours.

During the 14 day baseline phase patients in both groups took drug on average on 10 nights, and during the 28 day double blind treatment phase patients assigned to both placebo and drug arms took study medication about 17-18 times. 295 patients took at least 1 dose of study medication, and 274 completed study.

Primary Endpoint
Drs. Massey and Davis conclude that the primary endpoint was positive in favor of the zolpidem tartrate sublingual tablet at $p<0.0001$. LSO-MOTN for zolpidem was about 68 minutes at baseline and 38 minutes following the 4-week treatment period (30 minutes less), while the corresponding values for placebo were 69 and 56 minutes (13 minutes less). Each week individually was also nominally positive at $p<0.001$.

Dr. Massy finds that the primary analysis result seem robust to varying assumptions regarding missing data.

Secondary Endpoints
The following secondary endpoints were analyzed hierarchically.
1. Subjective Total Sleep Time post MOTN dosing (sTST-MOTN)
   This endpoint was negative, $p = 0.128$. Dr. Massey notes that this negative result might have been related to a baseline imbalance in TST, with baseline TST in the zolpidem arm about 18 minutes longer than TST in the placebo arm.
2. Subjective Number of Awakenings post MOTN dosing (sNAW-MOTN)
   This endpoint was nominally positive, $p <0.001$.
3. Subjective Wake Time after Sleep Onset post MOTN dosing (sWASO-MOTN)
   This endpoint was nominally positive, $p = 0.006$.

Dr. Massey notes that secondary endpoints 2 and 3, in addition to being below a negative endpoint in the hierarchical analysis, had inappropriate pre-specified analysis plans that did not fit the actual data, and were thus analyzed in a post-hoc manner.

CDTL conclusion, subjective study: The study supports the efficacy of the 3.5 mg dose of Intermezzo in adult patients.

Dose Exploration

(b) (4)

he sponsor bases this conclusion on findings from the PSG study, in which both doses were used in a crossover design. The sponsor states that the 3.5 mg dose induced sleep relatively faster than the 1.75 mg dose: about 14 vs. 24 minutes for LPS-MOTN (versus 37 for placebo), and about 34 vs. 38 minutes for SOL-MOTN.

Dose selection was also based on a PK/PD study, ZI-05-009, that examined the psychomotor effects of 1.0 mg, 1.75 mg, and 3.5 mg; little change was detectable for 1.0 mg on the psychomotor tests, with increasing effects at 1.75 and 3.5 mg.

CDTL: The PSG study, combined with phase 1 studies, indicates that the sponsor studied doses in the steep portion of the dose/response curve for zolpidem. The direct demonstration of efficacy in the PSG study of the 1.75 mg dose in adults suggests that the 1.75 mg dose could also be recommended in labeling as a starting dose in *adults*, not just elderly patients.

Subgroup Analysis

Age
FDA agreed that to support the dosing recommendation in the elderly, the exposure to zolpidem should fall between two safe and effective doses in non-elderly subjects. Data from the PK study in elderly (ZI-14) provide this evidence.

In the PSG study (ZI-06-010), the treatment effect appeared to increase slightly with age based on data from all three crossover periods. This result was of questionable robustness because the effect was not seen in analysis of the first period only.

In the subjective study (ZI-12), there was again the suggestion that the treatment effect may increase with age.

CDTL: While findings suggesting increased efficacy with age are not particularly robust, it is very unlikely that efficacy decreases with age. Since the 1.75 mg dose was effective in adults, this supports the likely efficacy of the 1.75 mg dose in elderly.

Gender
There was no compelling evidence of gender effect in either pivotal efficacy trial.

Race
Differences between race groups (Caucasion/African American/Other) were slight, and evidence for an interaction between race and treatment group relatively weak.

8. Safety

Dr. Carole Davis conducted the clinical review of safety. She found no significant safety concerns that would preclude approval. However she notes concern that residual zolpidem levels could pose any early-morning safety risk, particularly if Intermezzo is used with less than the recommended four hours of remaining sleep time, or if there was inadvertent repeat dosing on a subsequent awakening (see detailed discussion below under *Special Safety Concerns*).

Exposure
A total of 436 subjects received 3.5 mg zolpidem tartrate sublingual lozenge, 130 subjects received 1.75 mg, and 315 subjects received placebo. The longest exposure was 4 weeks in the subjective study, which examined only the 3.5 mg dose; for the long-term safety of the drug, the sponsor relies on the reference listed drug, Ambien.

Deaths and Serious Adverse Events (SAE)
There were no deaths, and the only SAE was in a patient in the screening phase (placebo use) of study ZI-12 who had not received study drug.

Dropouts/discontinuations
The only adverse event leading to dropout that occurred in more than one patient was headache (N = 2).

Oral irritation
Dr. Davis did not find any substantial evidence of clinically important oral mucosal changes from Intermezzo.

Common adverse events
Common adverse events in the 4-week study are discussed here as most relevant to labeling. Adverse events in PK, PD, and short-term efficacy studies were generally unremarkable, with the most common complaints being somnolence, headache, fatigue, dizziness, and nausea.

The following table of TEAE's is taken from Dr. Davis' table 28. Adverse events in ≥ 1% of patients that occurred more frequently in the zolpidem arm are listed individually.

MedDRA System Organ Class **Preferred Term**	**zolpidem SL 3.5 mg (n=150)**	**placebo (n=145)**
# of Subjects Reporting ≥1 TEAE	29 (19.3%)	28 (19.3%)
Gastrointestinal Disorders	**6 (4.0%)**	**3 (2.1%)**
Nausea	2 (1.3%)	1 (0.7%)
General Disorders and Administration Site Conditions	**5 (3.3%)**	**0 (0.0%)**
Fatigue	2 (1.3%)	0 (0.0%)
Nervous System Disorders	**7 (4.7%)**	**5 (3.4%)**
Headache	4 (2.7%)	2 (1.4%)

Laboratory evaluations
Findings in the 4-week study were unremarkable.

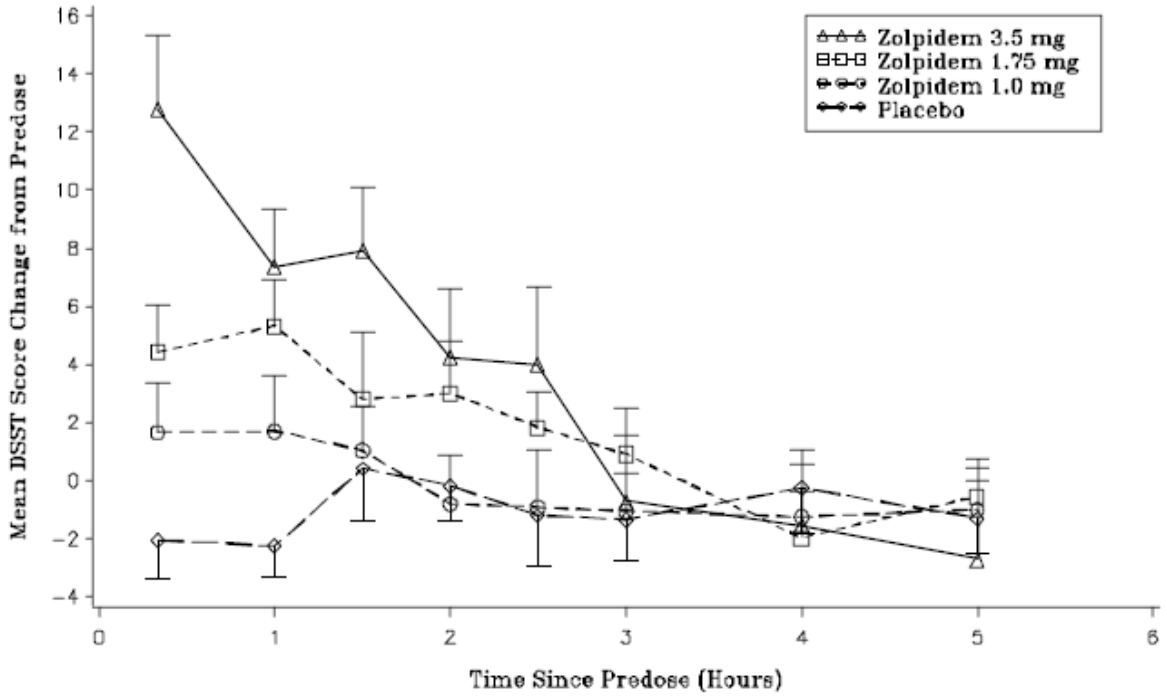
Vital signs
Vital signs were unremarkable, but focused on changes from baseline to 4-hours post-dose, and Dr. Davis notes that possible adverse effects near Tmax (e.g. orthostatic hypotension) could have been missed.

Residual/Next Day Effects
In the PSG study, a self-reported visual analogue scale of alertness and the Digit Symbol Substitution Test (DSST) were used to evaluate for residual sedation. Neither measure differed between placebo and the 3.5 mg or 1.75 mg Intermezzo arms.

In the outpatient study, morning sleepiness/alertness was measured on a 9-point scale. Patients dosing Intermezzo versus placebo felt themselves to be slightly 'more alert' (nominal p-value 0.03).

Study ZI-05-009 examined the PD effect of Intermezzo on the psychomotor test DSST during the day. DSST scores for the 3.5 mg and 1.75 mg doses returned to baseline at about 3 hours post-dosing (figure below).

Figure 11.2 **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.**



Cmax after a single dose of 3.5 mg zolpidem sublingual tablet was ~ 47 ng/mL. After 3 hours plasma concentration would be ~ 54% of Cmax, and 4 hours ~ 34% of Cmax. At ~ 6 hrs and 33 minutes plasma concentration would be 10% of Cmax.

CDTL: Residual effects were not detected with the tests used, but the sensitivity of these tests for clinically meaningful residual sedation is poorly characterized. For example, the DSST is conducted over just a few minutes, and is a poor reflection of the type of sustained attention that is needed for safe driving. However, as discussed immediately below, residual zolpidem levels at 4 hours are likely to be below levels that would be clearly associated with decreased driving performance.

Special Safety Concerns

Time of dosing

Morning blood levels of zolpidem from Intermezzo appear to be close to, but slightly below levels that are likely to represent a large safety risk from impaired driving. However, relatively small deviations in dosing time for Intermezzo could lead to impairment.

A recently published study by Leufkens et al. found that about 5- to 6 hours after a MOTN dose of 10 mg zolpidem (at 4 AM), driving performance was 'moderately impaired' by residual drug (Leufkens TR et al., *Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxodol,*

***zopiclone and zolpidem*. J. Sleep Res. 2009). Standard Deviation of Lateral Position (SDLP), a well-established measure of driving impairment, was increased by about 3.5 cm by zolpidem. The effect of ethanol was not examined, but the authors report that the change in SDLP from zolpidem was greater than that found for ethanol in other studies from a blood alcohol concentration of 0.5 mg/ml (2.5 cm), the legal limit for driving in many countries.**

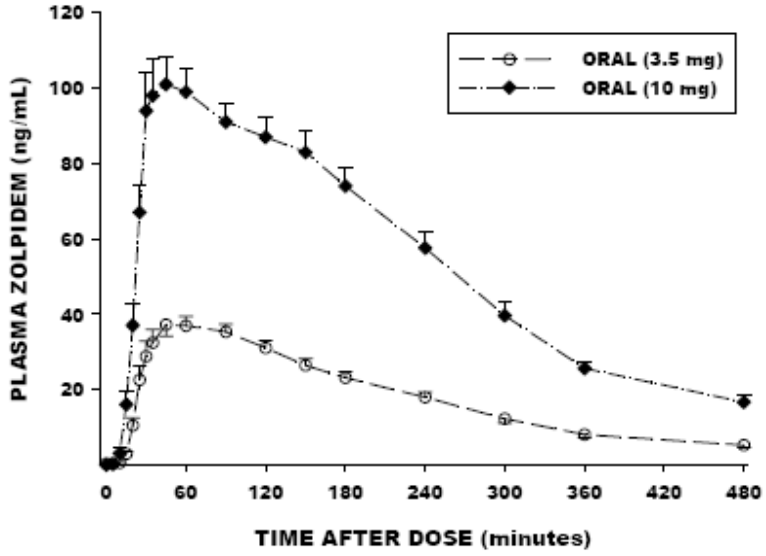
A study by Verster et al., (*Residual Effects of Middle-of-the-Night Administration of Zaleplon and Zolpidem on Driving Ability, Memory Functions, and Psychomotor Performance*. J. Clin Psychopharm 2002) found statistically significant impaired driving ability *4* hours after MOTN dosing of 10 mg zolpidem, but concluded that the magnitude of the impairment was small and 'not likely to be of clinical importance' This conclusion appears questionable because SDLP increased by about 3 cm, much greater than the increase of 1 cm associated with a blood alcohol concentration of 0.5 mg/ml in the study (it is unclear why the increase in SDLP from alcohol was lower in this study than in the study cited by Leufkins above, but the lower increase in SDLP from alcohol appears to *strengthen* the conclusion that the 3-fold larger increase in SDLP from zolpidem was clinically meaningful). Verster et al. was co-authored by employees of Wyeth-Ayerst (sponsor of zaleplon), raising concern for possible conflict of interest.

While the above comparisons of zolpidem to ethanol are concerning, it is important to note that SDLP captures only some aspects of impaired driving, and that the crash risk from zolpidem may differ from the crash risk from ethanol at similar levels of SDLP impairment; the correlation between SDLP and risk of traffic accidents from zolpidem has not been established.

The National Highway Transportation Safety Administration (NHTSA) is currently initiating a large case-control study to examine the crash risk associated with 'drugged driving.' This study will obtain blood samples from both drivers involved in crashes, and from 'control' drivers at the same site, thus providing a more reliable estimate of crash risk associated with specific drugs and drug levels. Previous studies of crash risk from sedative-hypnotics do not appear to provide adequate data to determine the risk from residual levels of zolpidem after taking Intermezzo.

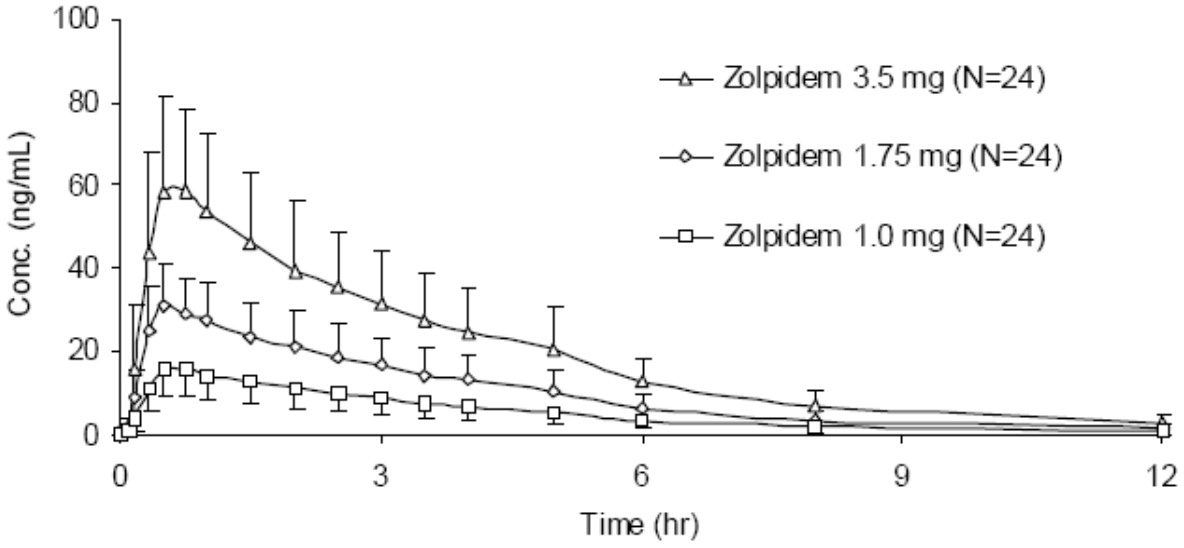
Zolpidem blood levels were not measured by either Leufkens et al. or Verster et al., but data from the current development program suggests that 6 hours after dosing of 10 mg Ambien, zolpidem blood level would be about 24 ng/ml (calculated by Dr. Parepally; see figure from study ZI-17 below).

Figure 9: Mean (±SE, n=35) plasma zolpidem concentrations for Study Part II.



The blood level 4 hours post dosing of intermezzo 3.5 mg would be lower, about 19 ng/ml (see figure from study ZI-05-009 below).

Figure 11.1 Mean (SD) Zolpidem plasma concentration-time profiles after administration of zolpidem 3.5, 1.75 and 1.0 mg.



Thus, if taken as directed, the zolpidem level from Intermezzo is likely to be somewhat below, but still close to the zolpidem level that was associated with moderate driving impairment. Of concern, if Intermezzo 3.5 mg is taken with only 3.5 hours of sleep remaining, blood levels would overlap those associated with impaired driving. In contrast, for the lower Intermezzo dose, 1.75 mg, by about 3 hours after dosing (or perhaps even earlier) the zolpidem level would be below the level of greatest concern.

The sponsor indicates that the current findings along with previous literature reports suggest that the zolpidem threshold concentration for the onset of sedation is about 20 ng/mL, and for the offset of sedation is about 25 ng/mL. This appears generally consistent with the above cited studies in driving.

Risk of dosing with less than 4 hours sleep remaining
While data was not collected in the Intermezzo development program specifically regarding the risk that patients would inadvertently dose Intermezzo with less than 4 hours of sleep time remaining, two lines of evidence indicate that such dosing occurs fairly frequently:

- **Seven subjects in the 4-week subjective study, 5 on zolpidem (3.3%), and 2 on placebo (1.4%), dosed after reporting that they had less than 4 hours of sleep remaining. The study was designed so that patients were required to call an interactive voice response (IVRS) system before dosing, and patients were given permission over the telephone to dose only if 4 hours were left of sleep time. These patients called the IVRS system, were denied permission to dose, but dosed anyway. It is not possible to differentiate purposeful disregard for the dosing instructions versus confusion on the part of the patients.**

- **Patients were instructed to call the IVRS system both before dosing, and about 30 minutes after awakening in the morning. About 2% of patients in each week of the study made the two calls separated by less than 4 hours, indicating the patients were presumably active less than 4 hours after dosing. There were no patients with calls separated by less than 3 hours.**

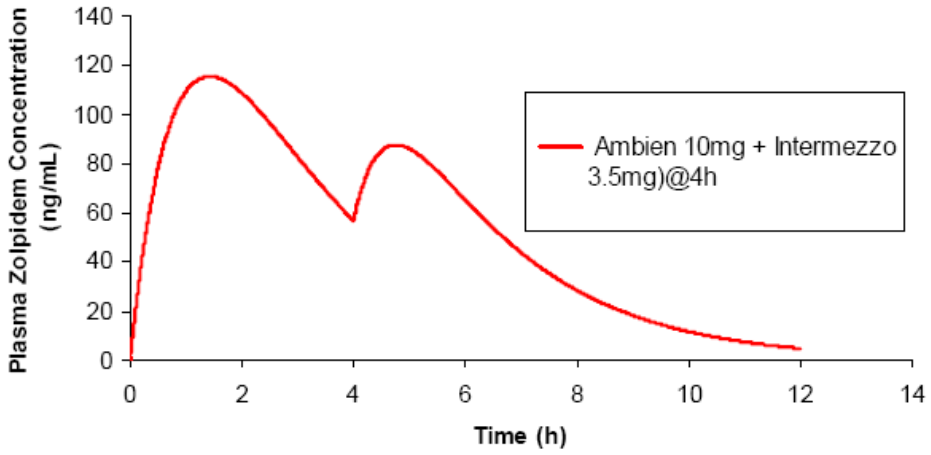
Few adverse events were reported overall in the study, and no correlation was apparent between adverse events and dosing with less than 4 hours remaining in bed. However, the power to detect adverse events associated with deviations from labeled dosing instructions was small.

The sponsor argues that there is a large body of evidence showing that patients with insomnia are hyper-aroused, and should be able to determine before taking Intermezzo if 4 hours of sleep time remain. The fact remains, however, that the outpatient study demonstrated that dosing with less than 4 hours of time in bed is not rare.

Concomitant Dosing With Ambien

Intermezzo would be labeled to be taken once/night, and not to be taken in combination with other sleep medication. Potentially, dosing of more than a single tablet each night, or dosing Intermezzo MOTN after taking Ambien 10 mg before bed could represent a safety risk.

Dr. Parepalli estimates that Intermezzo 3.5 mg taken 4 hours after Ambien 10 mg would result in the following concentration curve:



I conclude from this simulation that Ambien dosing at bedtime potentially increases zolpidem levels only modestly at wake time if both Ambien and Intermezzo are otherwise taken at the recommended times before waking. This level might result in impaired driving at 8 hours after Ambien dosing, at which time the blood level of zolpidem would still be about 25 ng/ml.

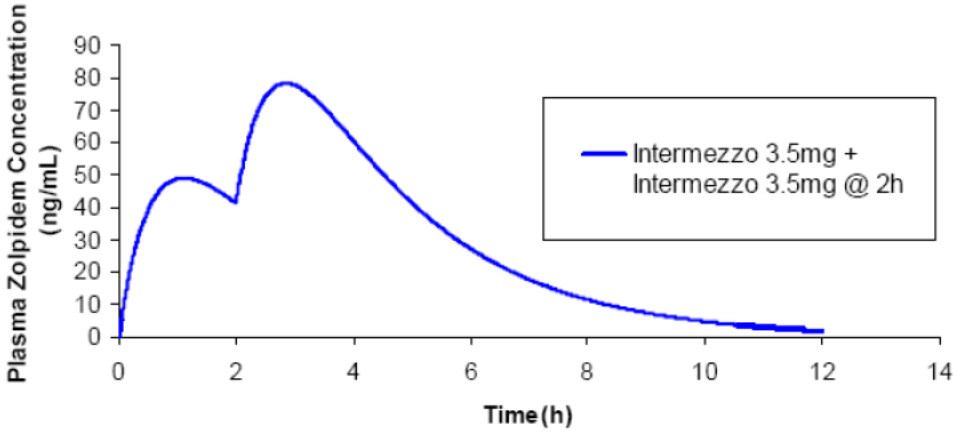
Repeat Dosing of Intermezzo

There were no reports of patients taking more than one dose of Intermezzo in the 4-week outpatient study, and no patient called the IVRS system twice in one night. This might suggest that the risk of inadvertent repeat-dosing of Intermezzo is relatively low. However, a high percentage of unaccounted-for doses of Intermezzo were recorded, and multiple-dose errors can not be excluded as a potential cause. Subjects were given a 2-week supply of study medication, and unused tablets were counted on return clinic visit. About 15% of patients had a deviation of ≥4 tablets from the expected number based on the IVRS record.

Zolpidem is known to interfere with cognition and memory. This pharmacodynamic activity could increase the risk of patients inadvertently taking a second tablet in a single night. Study ZI-05-009, a PK/PD study in normal volunteers, confirmed that 3.5 mg zolpidem can impair memory. Sleep itself is associated with amnesia; events occurring within 5 minutes of falling asleep are more difficult to remember. About 1% of doses of Intermezzo were followed by sleep onset within 5 minutes, potentially increasing the risk that patients would not remember if a dose was taken, and would take another dose on later awakenings.

In addition to the above drug- and sleep-specific factors potentially associated with repeat-dosing error, it seems plausible that 'normal forgetfulness' could result in patients inadvertently taking more than one dose per night.

Dr. Parepally estimated zolpidem levels if a second dose of Intermezzo 3.5 mg is taken 2 hours (an arbitrarily selected time) after a first:



Even if there are 4 hours remaining in bed after the second dose, blood level (about 25 ng/ml) at waking might result in impaired driving.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held.

10. Pediatrics

(b) (4)

The Division deferred studies in children 6- to 17-years old, and waived studies in children under 6 years old. The Division indicated that pediatric studies of Intermezzo should be conducted in children with Attention Deficit Hyperactivity Disorder (ADHD), in whom sleep abnormalities have been relatively well characterized.

11. Other Relevant Regulatory Issues

- *Division of Scientific Investigations*: Dr. Antoine El-Hage notes that two sites were inspected, and the data from both appear acceptable in support of the application.

- *Study Endpoint and Label Development* (SEALD): Ann Marie Trentacosti from the SEALD team reviewed several patient-reported outcome (PRO) instruments submitted in support of efficacy and safety. She concluded that none of the instruments were adequate assessments of either concept.
- *Controlled Substance Staff* (CSS): CSS review was not completed at the time of this review.
- *Proprietary name*: The Division of Medication Error Prevention and Analysis (DMEPA), does not object to the use of the proprietary name Intermezzo.

12. Labeling

I find that Intermezzo presents a risk of driving impairment if not taken as directed. I recommend that this risk be explicitly described in labeling.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
I recommend approval of Intermezzo, contingent on the following:

- Labeling that warns of potential for driving impairment.
- A postmarketing requirement to study risk of automobile crashes associated with Intermezzo.

Risk Benefit Assessment
Efficacy for sleep latency after MOTN awakening was clearly demonstrated for Intermezzo, and the safety profile appears acceptable if the drug is taken as directed. Concern remains, however, that deviations from taking the drug as directed could result in next-day residual zolpidem levels that impair driving performance and result in crashes.

Recommendation for Postmarketing Risk Management Activities
I recommend that a postmarketing study be required to evaluate the safety risk of car crashes related to MOTN use of Intermezzo. Normal pharmacovigilance methods would not be able to adequately evaluate this risk. The sponsor has proposed agreeing to a large-scale, phase 4, Health System database study/survey to evaluate any potential unique AEs associated with MOTN use of Intermezzo. The sponsor recognizes that such an evaluation would require appropriate comparator event rates, and that such comparator rates are currently not known.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22328	ORIG-1	TRANSCEPT PHARMACEUTICALS INC	ZOLPIDEM TARTRATE LOZENGE

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

/s/

RONALD H FARKAS
09/03/2009

CLINICAL REVIEW

Application Type	NDA 22-328
Application Number(s)	
Priority or Standard	Standard
Submit Date(s)	September 30, 2008
Received Date(s)	
PDUFA Goal Date	October 30, 2009
Division / Office	OND - DNP
Reviewer Name(s)	Carole L. Davis
Review Completion Date	August 3, 2009
Established Name	Zolpidem tartrate
(Proposed) Trade Name	Intermezzo
Therapeutic Class	Sedative hypnotic
Applicant	Transcept Pharmaceuticals
Formulation(s)	Sublingual tablet 3.5 mg, 1.75 mg
Dosing Regimen	One tablet per night, PRN
Indication(s)	Insomnia following middle-of-the-night awakening
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that this product be approved for use in the adult population for the short-term treatment of insomnia characterized by prolonged sleep onset following middle-of-the-night awakening. There were no significant clinical safety concerns that would preclude approval. The sponsor has met the Agency's requirements for a successful approval of this 505(b)(2) application by showing the bioequivalence of the sublingual formulation of zolpidem to the Reference Listed Drug (RLD) Ambien® (Zolpidem Tartrate) Tablets (NDA 19-908), and by providing adequate CMC related data. In both pivotal trials, zolpidem tartrate SL 3.5 mg and 1.75 mg tablets met their primary endpoints of reducing the time to resumption of sleep after a middle-of-the-night awakening, when compared to placebo. Additional endpoints reinforced the primary efficacy findings.

1.2 Risk-Benefit Assessment

The risk-benefit assessment is acceptable from the clinical review and the known profile of the referenced drug Ambien®. Although some specific risk:benefit concerns remain, the lower dose strength does provide a margin of safety when used as directed.

The zolpidem tartrate sublingual (SL) 3.5 mg and 1.75 mg products were evaluated in this NDA submission. The proposed tradename is Intermezzo. Due to the designation for middle-of-the-night use, the doses are lower than the approved reference drug (Ambien® 10 mg and 5 mg), and have a very similar excretion half-life (~2.6 hours for all the dosages). Review of data relating to the sublingual administration of the drug raised no concerns. The sponsor proposes a labeling recommendation for use of the drug once a night, as needed (PRN), if at least four (4) hours of bed time remains before morning activities.

This would be the first insomnia drug to be marketed for that indication of middle-of-the-night, insomnia. The concern raised is whether the medication will pose any early-morning safety risk, particularly if used with less than the recommended four hours of remaining sleep time. Since the medication would probably be kept at bedside, there is also the possibility of inadvertently repeating the dose on a subsequent awakening. These concerns are addressed in Section 7.7.

The pivotal (Phase 3) trials did not address pharmacokinetic (PK) or pharmacodynamic (PD) issues in the time between dosing and a recommended $\geq$ hour 4 awakening. The early phase PK/PD trials were designed primarily to investigate the parameters for the first hour post-dose, and the hour 4 endpoint. So, there is a scarcity of data on the effects of the drug between hour 1 and hour 4 post-dose to evaluate the safety risk of using the drug without 4 hours of additional bedtime. However, in Study ZI-05-009, the pharmacodynamic (PD) scores of the various tests indicate that the zolpidem SL 3.5 mg can have statistically significant PD effects, compared to placebo, up to 1.5 hours on the Digit Symbol Substitution Test (DSST), and to 3 hours on the

Choice Reaction Time (CRT). The 1.75 mg dose shows significant changes to 1.5 hr. on the DSST, but only to 20 minutes on the CRT. Neither dose showed significant effect on the Buschke Word Recall Test (BMR) or Symbol Copying Test (SCT) at any time interval. The 1.0 mg dose (tried only in early trials) has no effect on most of the measurements. The subjects' self-rated Visual Analog Scale (VAS) scores indicate a subjective drug effect on sleepiness/alertness of up to 2 hours duration for both the 3.5 and 1.75 mg doses, and no effect for the 1.0 mg dose of zolpidem SL. The PD measurements chosen may not be sufficiently sensitive to evaluate morning residual effects (especially for sustained attention or reflexes/co-ordination psychomotor skills), and subject self-assessment of alertness/sleepiness may not be reliable due to residual drug effects or which the subjects are unaware.

The short-comings of the development program for zolpidem tratrate SL 3.5 mg and 1.75 mg include the lack of pharmacodynamic data in the elderly, traditionally a major component of the consumer market for sleep aid products; only a Phase 1 pharmacokinetic (PK) trial included subjects $\geq$ 65 years. Also, in all trials there is a lack of middle-of-the-night data (postural stability, reflexes, and orthostatic hypotension checks), sensitive early morning data (especially driving assessment), and assessment for "late-day slump".

Overall, the clinical trials have established the efficacy for treatment of middle-of-the-night sleep latency, the safety profile, when used as directed, is acceptable, and the lower doses are less likely to be abused.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Agency indicated to the sponsor, Transcept, that a Risk Evaluation Mitigation Strategy (REMS) is required for this medication. Transcept submitted a REMS Supporting Document, and plans to submit a REMS proposal including a Medication Guide to highlight dosing instructions, and possible risks of middle-of-the-night dosing. A Knowledge, Attitudes and Behavior (KAB) Survey will be carried out at required timepoints (18 months, 3 years, and 7 years) to evaluate the effectiveness of the Medication Guide instructions. Transcept also proposes to incorporate expedited reporting in periodic quarterly and annual safety reports of "Events of Interest" for the MedRA preferred terms possibly related to medication errors.

I recommend that a carton containing individual blisters would be preferable for safety. The carton could be kept in a medicine cabinet, and a single dose left at bedside each night. If a tablet is used, then on a subsequent awakening, there would be the evidence of an individual empty blister package to remind the patient.

1.4 Recommendations for Postmarket Requirements and Commitments

[redacted] The division has requested that Transcept consider conducting pediatric trials for this product. Although Ambien® at 5 mg and 10 mg doses did not show efficacy and had an unacceptable risk-benefit ratio for use in children and adolescents, there may be advantages to use of the lower dose formulation. It may have efficacy with lower risk of adverse events, and allow treatment of insomnia only when it occurs, rather than prophylactic nightly treatment.

2 Introduction and Regulatory Background

2.1 Product Information

The zolpidem tartrate sublingual tablet is a non-benzodiazepine hypnotic of the imidazopyridine class. It is a short-acting non-benzodiazepine hypnotic that potentiates gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to $GABA_A$ receptors at the same location as benzodiazepines.

Zolpidem has a preferential binding for the $GABA_A$-benzodiazepine receptor complex in the brain (BZ_1) but a low affinity for the $GABA_A$-benzodiazepine receptor complex in the spine (BZ_2).

The chemical formula is $C_{19}H_{21}N_3O$, and the systematic (IUPAC) name is [redacted] Bioavailability is 70% (oral), and 92% bound in plasma. Excretion is 56% renal, 34% fecal, and CYP3A4 hepatic metabolism.

The inactive ingredients in the zolpidem tartrate SL include: mannitol, colloidal silicon dioxide, [redacted] croscarmellose sodium, [redacted]

The indication is for use as needed for the treatment of insomnia characterized by middle-of-the-night (MOTN) awakening with difficulty returning to sleep. [redacted] sublingually once nightly as needed. The recommended dose for elderly or debilitated patients, or for patients with hepatic insufficiency, is 1.75 mg once nightly, as needed. The recommended total daily dose of Intermezzo should not exceed 3.5 mg. The medication should be administered only when at least 4 hours of time in bed remains, and should not be administered with or immediately after a meal. Packaging plans include [redacted] It is classified as a Schedule IV drug, and pregnancy category [redacted]

For this application, the sponsor relies on the referenced listed drug Ambien (zolpidem tartrate) 10 mg and 5 mg (NDA 19-908). The treatment rationale is that use of an as-needed middle-of-the-night hypnotic could reduce the reliance on higher dose hypnotics used by patients at bedtime to prevent awakenings that might not occur (i.e., PRN rather than prophylactic use).

Onset of action is short, generally estimated at 10-20 minutes, and the half-life is estimated at ~ 2.5 hours. Trade names (US and overseas) of zolpidem tartrate include Adormix, Ambien, Ambien CR, Edluar, Damixan, Ivedal, Nytamel, Stilnoct, Stilnox, Sucedal, Zoldem, Zolnod and Zolpihexal. Edular is another zolpidem tartrate sublingual drug (NDA 21-997) recently approved for short-term insomnia at 10 mg for use at bedtime.

2.2 Currently Available Treatments for Short-term Insomnia

There are no other sedative-hypnotic products approved on the American market for middle-of-the-night insomnia.

Products for the short-term treatment of insomnia in adults (all recommended for use at bedtime) include benzodiazepines, anticholinergic antiemetics and antihistamines, miscellaneous anxiolytics, analgesic combinations, tricyclic antidepressants, and barbituates. No sedative-hypnotics have been approved for treatment of insomnia in children.

In addition to the Ambien products, some of the FDA-approved sedative-hypnotics for the same indication are Halcion (triazolam), Prosom (estazolam), Ambien (zolpidem), Sonata (zaleplon), Restoril (temazepam), and Lunesta (eszopiclone). Ramelteon, a melatonin receptor agonist is also approved.

The sponsor has sought the claim of treatment for middle-of-the-night insomnia as a distinct primary complaint from sleep maintenance based on the following assertion:

> *Sleep maintenance insomnia is characterized as excessive wakefulness anytime after sleep onset, and can be characterized by multiple short awakenings, a few prolonged awakenings, or both. Treatment occurs prior to bedtime, and wake time after sleep onset (WASO) is the efficacy measurement. MOTN insomnia is characterized by insomnia occurrence in the first half of the night with a prolonged period of wakefulness, and the efficacy measurement proposed is latency in return to sleep.*

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate was initially approved as an immediate-release formulation under the trade name Ambien® (NDA 19-908) by Sanofi-synthelabo. The recommended dosing at bedtime, as needed, for the short-term treatment of insomnia due to delayed sleep onset is 10 mg for adults, or 5 mg for patients older than 65 years or those with impaired hepatic function. Ambien CR™, a bilayer formulation for immediate and sustained release, was approved in 2005 (NDA 21-774) for treatment of delayed sleep onset, and/or sleep maintenance. The recommended dosing is 12.5 mg for adults, 6.25 mg for elderly patients. Recently (March, 2009), Edular, a 10 mg

zolpidem tartrate sublingual tablet was approved (NDA 21-997). The FDA approved 13 generic versions of zolpidem tartrate in April, 2007.

2.4 Important Safety Issues with Non-Benzodiazepine Drugs

The FDA has recently requested (March, 2007) that manufacturers of sedative-hypnotic sleep medicines put stronger warning labels on their products to increase awareness of the potential risks. These include severe allergic reactions, abnormal thoughts and behavior, and dangerous sleep-related behaviors, including sleep-driving.

The non-benzodiazepines drugs are generally considered less likely to be addictive than benzodiazepines, but must still be used with caution because abuse or dependence can occur. Overdose with the medication is possible, and combination with alcohol, opiates or other CNS depressants increases the risk of adverse effects. Alcohol has cross tolerance with $GABA_A$ receptor-positive modulators such as the benzodiazepines and the non-benzodiazepine drugs, so alcoholics, or recovering alcoholics, may be at increased risk of physical dependency on zolpidem.

In previous clinical trials for Ambien, the risks associated with the recent labeling warnings were generally dose-dependent. The risks significantly increased with dosing > 10 mg. The current application for zolpidem tartrate SL proposes recommended doses of 3.5 mg or 1.75 mg for middle-of-the-night use. There is not yet enough information available to determine how the lower doses, and their timing, affect the previously noted risks for the drug.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

On June 22, 2007, TransOral Pranaceuticals, Inc. notified the FDA of a change in their company name to Transcept Pharmaceuticals, Inc. Pre-NDA development on low-dose zolpidem tartrate SL was done under IND 69,209.

December 22, 2004 –Type D/Pre-IND Meeting with TransOral Pharmaceuticals, Inc.to discuss the preparation of the IND submission and clinical development plan.
Discussion focused of differences that distinguish the claim for MOTN insomnia from sleep maintenance, drug bioavailability data, and assessment for local tissue reaction. The Agency agreed that if Cmax and AUC for the drug do not exceed those of the currently recommended doses of Ambien, no further toxicology and abuse liability studies would be needed.

January 10, 2006 – Type C Meeting with TransOral Pharmaceuticals, Inc. to discuss development plans for supporting a claim for middle-of-the-night (MOTN) insomnia.
Agreements included discussion on the following topics:

- The Agency would like to see a secondary endpoint evaluating whether patients remain asleep, a statistically significant difference on this endpoint is not a requirement for establishing the effectiveness of a claim for insomnia characterized by MOTN awakening.

- Two doses (3.5 mg and 1.75 mg) will be studied in the Phase 3 PSG study. If the safety profiles of the two doses are similar, the higher dose would be approved for adult non-elderly use.
- The duration of the proposed study, which is intended to support (b) (4)

In the subsequent correspondence (March 16, 2006 letter), TransOral requested clarification on the following issues:

- In the course of the meeting the Agency agreed that a single-dose pharmacokinetic (PK) study would be sufficient for approval in the elderly population as stated in the "Action Items" section. However the Agency's draft minutes state that "The Agency will require that the sponsor provide data regarding clinical effects in the elderly, including next day residual effects."
- The Agency's requirement that TransOral agreed to complete a daytime food effect study on the highest strength tablet in healthy adults, and
- TransOral's agreement to submit a proposal for a Phase 4 study evaluating interactions of zolpidem SL with bedtime hypnotics.

A review of subsequent letter correspondence did not reveal a follow-up to the question dealing with data on clinical effects in the elderly.

June 19, 2007 – End of Phase 2 Chemistry, Manufacturing and Controls Meeting with Transcept to discuss proposed composition, specifications, and stability plan for filing including agreements on the (b) (4) and submission of stability data.

April 2, 2008 – Meeting with Transcept Pharmaceuticals, Inc. to discuss clinical development plans.

Included in the NDA submission (b) (4)

The Division of Medication Error Prevention and Analysis previously reviewed the proposed proprietary name, Intermezzo, in OSE Review 06-0129, dated January 11, 2007 and had no objections to the use of the name at that time.

DMEPA notes that in a letter from the Division to the Applicant, dated December 11, 2008, CMC had the following comments concerning the established name (b) (4) The established name should refer to this drug product as a sublingual tablet."

2.6 Other Relevant Background Information

The sponsor underwent a change of name during the course of the clinical development of the product. The early IND trials were conducted under the sponsor name TransOral Pharmaceuticals.

Trials were conducted with two formulations of the zolpidem tartrate sublingual tablets. The bridging trial is discussed in Section 4.4.3. The pivotal trials used different formulations; ZI-06-010 used the IND formulation, and ZI-12 used the commercial formulation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The following sites were selected for inspection based on number of enrolled subjects:
Yuri Furman, M.D., Los Angeles, CA – Study ZI-12
D. Alan Lankford, Ph.D., Sleep Disorder Center of Georgia, Atlanta, GA – Study ZI-06-010 and ZI-12

The medical records/source documents for subjects selected for review included appropriateness of randomization, informed consent, drug accountability, laboratory records, IRB records, and source documents. These were compared to case report forms and data listings, including primary efficacy endpoints and adverse events. The conclusion from the review of the establishment inspection reports and the documents submitted with the reports, was that the sites adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations, and the protection of human subjects. The FDA reports were reviewed and filed by Antoine El-Hage, Pharmacologist, DSI.

3.2 Compliance with Good Clinical Practices

The DSI reports state that the sites appear to have been in compliance with good clinical practices (GCP).

3.3 Financial Disclosures

Transcept submitted certification of the absence of disclosable interests (form 3454) for the majority of the principal investigators and their sub-investigators. Financial disclosure information from the principal and sub-investigators for the pivotal trials was submitted.

In accordance with 21 CFR 54.2 Transcept disclosed financial agreements (form 3455) with the following investigator:

[redacted] provides consulting services on an ongoing basis for investigational products in development, and has received payment in excess of $25,000 for these services". The laboratory of [redacted]

Transcept cites the following measures taken to minimize potential bias: [redacted] did not participate directly in the clinical conduct of either trial, and did not have access to any unblinded data prior to database lock and completion of data analysis, according to the signed statistical analysis plan.

Pursuant to 21 CFR 312.52, TransOral Pharmaceuticals Inc. submitted a list of obligations transferred to [redacted] including data collection and management to [redacted] and site management and monitoring, to [redacted] for study protocol ZI-06-010. For protocol ZI-12, both data collection and management, and site management and monitoring was transferred to [redacted] For both pivotal trials, pharmocovigilance/safety was transferred to [redacted]

Conclusions and Comments
The submitted financial information is complete. The payments made to [redacted] were unlikely to have influenced the trial outcomes if he did not receive unblended data. The data from the [redacted] was consistent with the results for the other sites.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A CMC review is being performed by Martha R. Heimann, Ph.D.
The following comments are based upon her preliminary conclusions. A detailed CMC review will be filed separately.

Prior to submission of the NDA, Trancept sought CMC advice via the pre-IND meeting held on November 16, 2004 (with HFD-170), the CMC End of Phase 2 meeting held on June 19, 2007 and a Type C meeting request (written response provided). Most of the questions that were raised by the sponsor during these discussions were deferred as review issues. One significant issue was identified, however. The proposed commercial formulation includes a noncompendial excipient, [redacted] Since it is a [redacted] it is considered a novel excipient by CMC.

[redacted]

The 3.5 mg and 1.75 mg zolpidem tartrate SL tables are tablets are round, uncoated, biconvex, and debossed with ZZ on one side, blank on the reverse side. The two strengths are distinguished from each other by color. The 3.5 mg tablet is beige, and the 1.75 mg tablet is yellow. The manufacturing firm is [redacted] (b) (4) under DMF [redacted] (b) (4) The DMF has previously been reviewed and considered acceptable.

The Office of Biostatistics has performed a statistical analysis of the stability data and determined that the 12-month data are within specifications and additionally support extrapolation to 18 months, though not the 24-month expiry period requested by the sponsor.

4.2 Clinical Microbiology

Not applicable for this NDA review.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data was submitted with this NDA. As a 505(b)(2) submission, the sponsor relied on the non-clinical data previously submitted for the referenced approved drug, Ambien® 10 mg and 5 mg.

The following material is taken directly from the approved Ambien® labeling:

> ***Carcinogenesis, mutagenesis, impairment of fertility***
> ***Carcinogenesis:*** *Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10 mg human dose on a mg/kg or mg/m2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10 mg human dose on a mg/kg or mg/m2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.*
>
> ***Mutagenesis:*** *Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.*
>
> ***Impairment of fertility:*** *In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m2. No effects on any other fertility parameters were noted.*

4.4 Clinical Pharmacology

The clinical pharmacology/biopharmaceutical review is being performed by Jagan Mohan Parepally, Ph.D. and will be filed separately. The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 22-328 and considers the submission acceptable pending agreement of labeling recommendations in the package insert. Their review did not make recommendations for Phase IV commitments.

The following were included in the Clinical Pharmacology review of this NDA:

- Three single-dose pharmacokinetic (PK)/ bioequivalence (BE) bridging studies in healthy adult and elderly subjects. Study ZI-15 is the pivotal bioequivalence study comparing the single-dose PK of the 3.5 mg tablet to the 10 mg reference Ambien® tablet, and included the effect of food on drug absorption. Study ZI-14 includes comparative bioavailability of Intermezzo 1.75 mg and 3.5 mg in elderly and adult cohorts. Study ZI-13 is a formulation bridging study to link the IND formulation to the final commercial formulation. Final commercial formulation was used in most of the studies including pivotal BE, pharmacodynamic, and efficacy studies.

- Three single dose placebo-controlled pharmacodynamic studies in healthy subjects (study ZI-05-009, ZI-16 and ZI-17).

- Four pilot studies conducted before initiation of the IND 69,209, and were considered exploratory in nature. The studies include ZI-04-001-001, ZI-04-002-002, ZI-04-003-003, ZI-04- 07, all of which used higher doses (10 mg) of zolpidem.

Several of the studies were 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

4.4.1 Mechanism of Action

From the Ambien® label:

> *Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.*
>
> *While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, 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. In contrast to the benzodiazepines, which non-selectively bind to*

and activate all omega receptor subtypes, zolpidem in vitro binds the (ω1) receptor preferentially with a high affinity ratio of the alpha1/alpha5 subunits. The (ω1) 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 (ω1) 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 at hypnotic doses.

4.4.2 Pharmacodynamics

The active ingredient of zolpidem tartrate sublingual 3.5 mg and 1.75 mg is the same as the referenced approved drug, Ambien® 10 mg and 5 mg respectively, but with a 65% lower dose, and 38% of the bioavailability.

Reviewed with this NDA were two Phase 1 pharmacokinetic/pharmacodynamic (PK/PD) trials:

- Study ZI-05-009 – PK/PD, safety and dose-proportionality of 3 dosage strengths of zolpidem tartrate SL tablet vs. placebo were evaluated.
- Study ZI-16 – Comparative PD effects and late PK effects of sublingual vs. oral dosing with the zolpidem tartrate SL tablet were evaluated.

In addition, another early PK trial, Study ZI-17, briefly addressed PD while evaluating sublingual vs. oral dosing for zolpidem 3.5 mg, and comparison to Ambien 10 mg. The trial evaluated PD changes by AUC to indicate the correlation between the formulations.

Study ZI-05-009 – Comparison of zolpidem SL 3.5 mg, 1.75 mg and 1.0 mg
Study ZI-05-009 is a randomized, double-blind, placebo-controlled, daytime, 4-way crossover trial to evaluate the PK, PD, dose proportionality, safety, and tolerability of 3 dose strengths (1.0 mg, 1.75 mg, and 3.5 mg) of zolpidem SL tablets on daytime sedation in 24 healthy volunteers (ages 21 to 45 years). Study drugs were administered on 2 successive days for each treatment period (washout of 5 -12 days between). Study drug was administered at 8 am after an overnight fast, and food was not provided until after the hour 5 PD testing. PK samples were obtained for 12 hours post-dose.

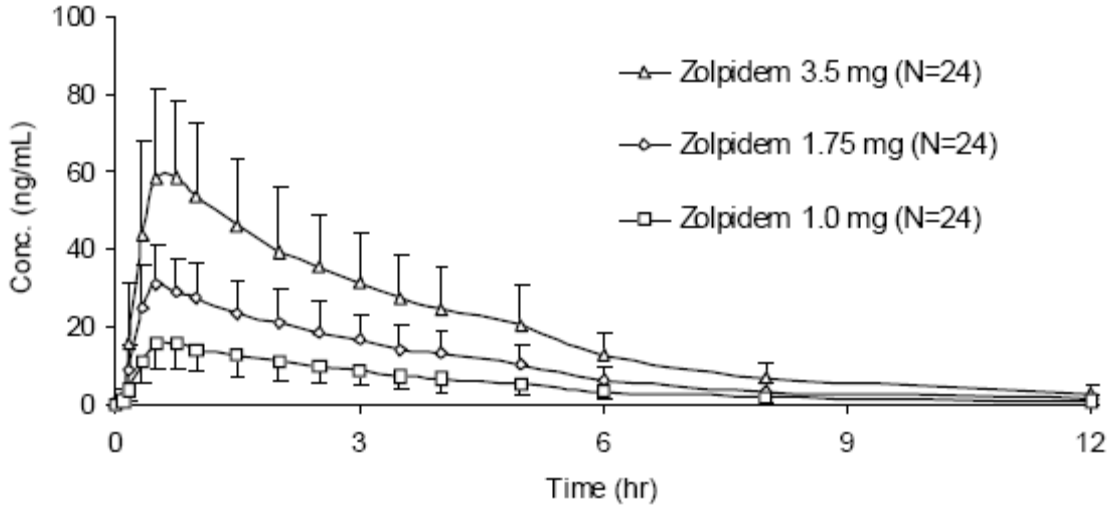
PK Results:
PK data showed a plasma concentration of 20 ng/mL within 20 minutes, and Cmax of 64 ng/mL and 32 ng/mL for the 3.5 mg and 1.75 mg doses, respectively. Tmax and $t_{1/2}$ remained stable over the doses, with a Tmax of ~ 36 minutes, and a $t_{1/2}$ of ~ 2 ½ hours (Table 1 and Fig. 1). The results, by LS mean ratios, show a consistent dose-proportionality for the 3.5mg and 1.75 mg dose strengths, but not the 1.0 dose.

Table 1. Mean (SD) zolpidem plasma PK parameters after administration of zolpidem tartrate SL 3.5, 1.75 and 1.0 mg - Study ZI-05-009

Parameter	Treatment		
	zolpidem 3.5 mg (N=24)	zolpidem 1.75 mg (N=24)	zolpidem 1.0 mg (N=24)
C_{max} (ng/mL)	64.1 (22.4)	32.2 (10.4)	17.0 (6.8)
T_{max} (h)	0.63 (0.2)	0.63 (0.3)	0.58 (0.2)
AUC_{0-t} (ng.h/mL)	229.5 (91.9)	119.6 (49.0)	62.6 (29.1)
AUC_{0-inf} (ng.h/mL)	242.6 (100.4)	126.1 (53.4)	66.2 (31.5)
$t_{½}$ (h)	2.4 (0.6)	2.4 (0.6)	2.3 (0.8)

Source: Clinical Study ZI-05-009, Section 14.2

Fig. 1 Mean (SD) Zolpidem plasma concentration-time profiles after administration of zolpidem 3.5, 1.75 and 1.0 mg.



Source: Study ZI-05-009, Section 14.4

PD Results:
The PD effects of zolpidem tartrate SL compared to placebo were investigated using the Digit Symbol Substitution Test (DSST), Choice Reaction Time (CRT), Symbol Copying Test (SCT), self-rating of sedation on a Visual Analog Scale (VAS), and the Buschke Memory Recall Test. Descriptions are provided in Appendix Table 3. The CRT is composed of the average response time mean score change, number of lapses in the CRT, and number of errors made. The results are listed in Table 2. The scores (#1-5, see footnote) reflect the testing time post-dose that test scores for the zolpidem group were statistically significantly different from the placebo group scores.

Table 2. PD results for 3 dosage strengths of zolpidem tartrate SL- Study ZI-05-009

Dose	DSST*	CRT*			BMR*	SCT*	VAS*
		change in mean rxn time	# lapses	# errors			
3.5 mg	1 2 3	1 2 3	1 2 3 4	1 5	1	0	1 2 3 4
1.75 mg	1 2 3	1	1	0	0	0	1 2 3 4
1.0 mg	0	0	0	2	0	0	0

*Results significantly different from placebo at post-dose time of: 1 = 20 min., 2 = 1 hr., 3 = 1.5 hr., 4 = 2 hr., and 5= 3 hr. 0 = no significance difference from placebo at any post-dose testing time

The PD scores of the various tests indicate that the zolpidem SL 3.5 mg can have statistically significant PD effects up to 1.5 hours on the DSST, and to 3 hours on one section of the CRT, with short to no effect on the BMR and SCT. The 1.75 mg dose shows significant changes to 1.5 hr. on the DSST, but only to 20 minutes on the CRT, with no significant effect on the BMR or SCT. The 1.0 mg dose has no effect on most of the measurements. The subjects' self-rated VAS scores indicate a drug effect on sleepiness/alertness for up to 2 hours for both the 3.5 and 1.75 mg doses, and no effect for the 1.0 mg dose of zolpidem SL. No significant residual effects were seen in scores by 3-4 hours post-dose.

The PD findings correlate fairly closely with the AUC analysis of PK parameters of the zolpidem groups compared to placebo group. The zolpidem plasma concentration declined rapidly ~30 minutes post-dose, and was 30-20 ng/mL by 4 hours post-dose which corresponded to a return to baseline scores for DSST and VAS measurements.

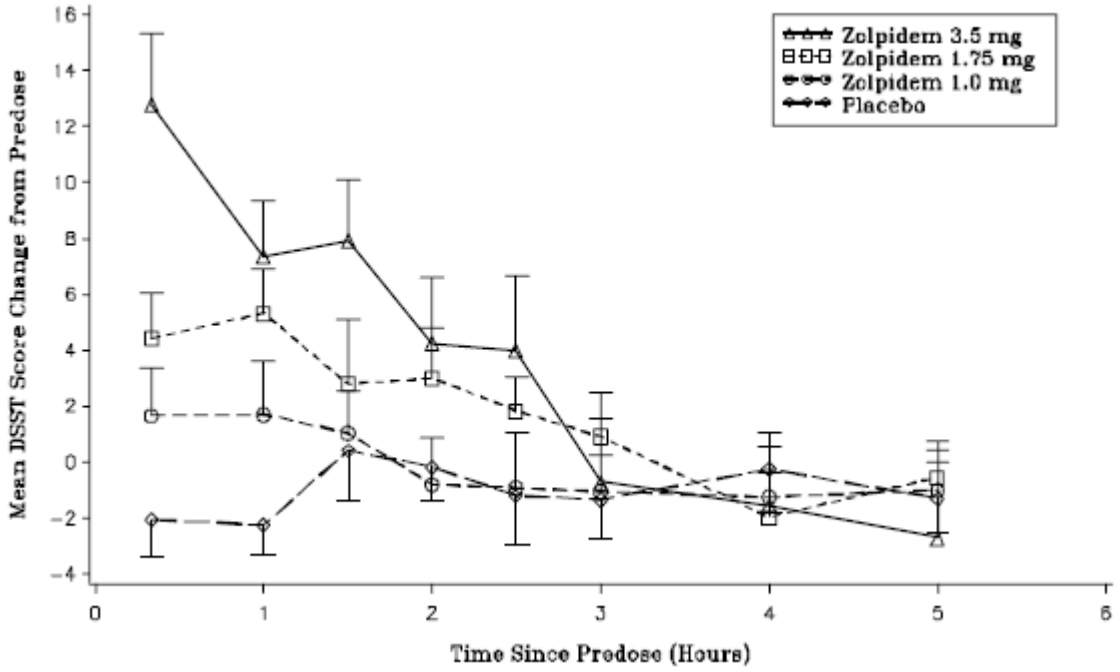
Table 3 summarizes the DSST scores, and the change in scores from the pre-dose scores. The results indicate that for the zolpidem 3.5 mg group at 2 hours and 2.5 hours, scores are still ~ 4 points lower than baseline. That represents less than a third (<1/3) of the maximum decrease in scores (experienced at 20 minutes post-dose). By hour 3 testing, for the 3.5 mg group, DSST scores are higher than the baseline score, and similar to changes for the placebo group (Fig. 2).

Table 3. DSST Score and Change in Scores from Baseline – ZI-05-009

Time	**DSST Score and Change from Baseline** (n = 24)								p-value	
	zolpidem 3.5 mg		zolpidem 1.75 mg		zolpidem 1.0 mg		placebo			
	Score	Change	Score	Change	Score	Change	Score	Change	3.5 mg	1.75 mg
Baseline	56.9		58.4		58.0		57.6			
20 min.	44.1	12.8	54.0	4.4	56.3	1.7	59.6	-2.0	<0.0001	0.013
1 hr.	49.5	7.4	53.1	5.3	56.3	1.7	59.8	-2.3	<0.0001	0.001
1.5 hr.	49.0	7.9	55.6	2.8	57.0	1.0	57.2	0.4	0.014	0.395
2 hr.	52.7	4.3	55.4	3.0	58.8	-0.8	57.8	-0.2	0.058	0.169
2.5 hr.	52.9	4.0	56.6	1.8	58.9	-0.9	58.8	-1.2	0.066	0.267
3 hr.	57.6	-0.7	57.5	0.9	59.0	-1.0	58.9	-1.3	0.643	0.336
4 hr.	58.5	-1.5	60.4	-2.0	59.3	-1.3	57.8	-0.3	0.896	0.925
5 hr.	59.6	-2.7	59.0	-0.5	59.0	-1.0	58.9	-1.3	0.907	0.631

Note: positive values represent greater sedation relative to pre-dose. Source: Clinical Study ZI-05-009, Section 14.4

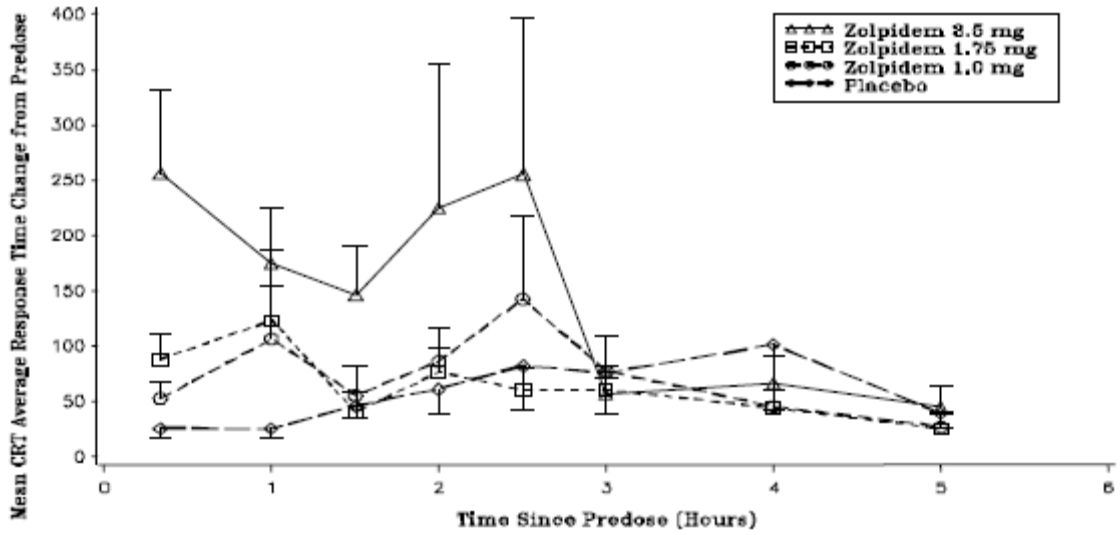
Fig. 2 Mean DSST score change from pre-dose by timepoint following administration of zolpidem 3.5 mg, zolpidem 1.75 mg, zolpidem 1.0 mg, and placebo - Study ZI-05-009



Source: Study ZI-05-009, Section 14.4

Comparisons of the average response time mean score change vs. placebo in the CRT indicated statistically significant differences at 20 min, 1.0 hr, and 1.5 hr for the zolpidem 3.5 mg group; at 20 min for the zolpidem 1.75 mg group; and at no timepoint for the zolpidem 1.0 mg group (Fig. 3).

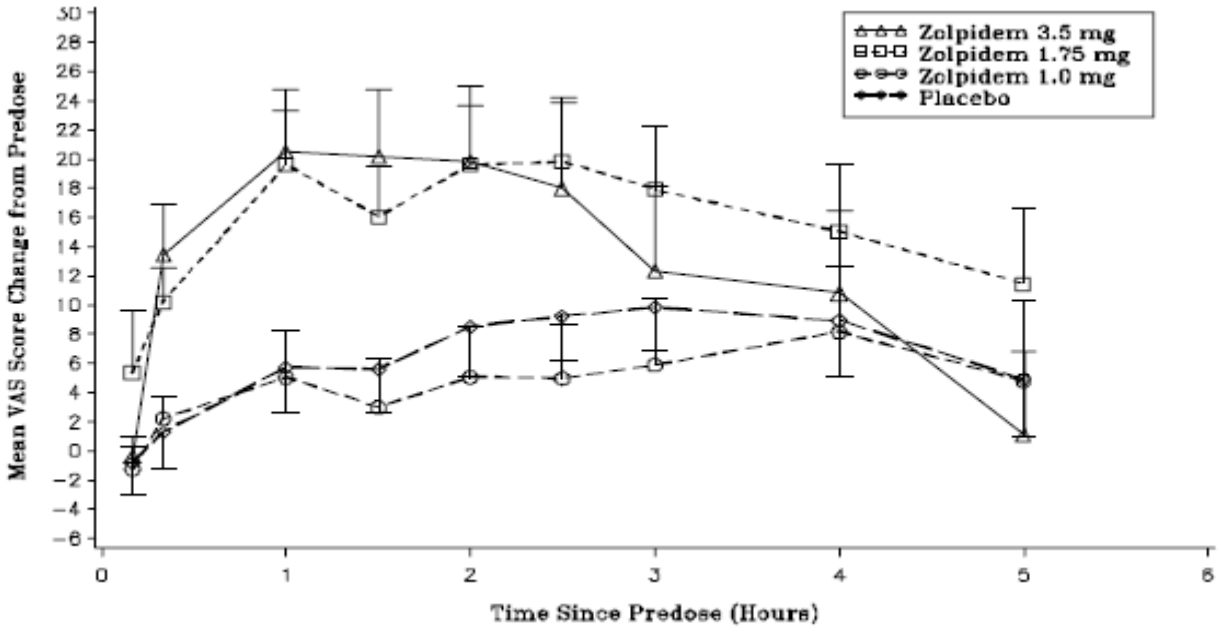
Fig. 3 Mean CRT average response time change from predose by timepoint for zolpidem SL 3.5 mg, 1.75 mg, 1.0 mg, and placebo - Study ZI-05-009



Source: Study ZI-05-009, Section 14.4

Analysis of VAS mean score changes (indicating subjectively experienced effects of the drug) shows statistically significant differences, compared with placebo, at 20 min, 1.0 hr, 1.5 hr and 2.0 hr for both the zolpidem 3.5 mg and 1.75 mg treatment groups (Fig. 4). By hour 3 testing, the zolpidem 3.5 mg group was similar to the placebo group in VAS scores, but the scores for the 1.75 mg group remained elevated with no apparent explanation for the difference. There were no statistically significant differences between the zolpidem 1.0 mg and placebo groups at any timepoint.

Fig. 4 Mean VAS score change from predose by timepoint for zolpidem SL 3.5 mg, 1.75 mg, 1.0 mg, and placebo - Study ZI-05-009



Source: Study ZI-05-009, Section 14.4

The Buschke Word Recall test, showed a statistically significant change from baseline scores (compared with placebo) at only 20 min for the zolpidem 3.5 mg group. The SCT showed no statistically significant differences at any timepoint for any group compared with placebo. The partial AUC analyses showed similar results.

Safety Results:
Total AE incidence was 71%, 54%, and 29% in the zolpidem SL 3.5, 1.75 and 1.0 mg groups respectively, and 46% in the placebo group. The most commonly reported AE was somnolence (42%, 12%, 21% in the 3.5, 1.75 and 1.0 mg zolpidem groups respectively, and 12% in the placebo group). Nausea was reported by 3 subjects, and vomiting by 1 subject, in the 3.5 mg group only. There were no serious AEs (SAEs), and no subjects were discontinued due to an AE.

Comments and Conclusions:
PK: The zolpidem SL 3.5 mg and 1.75 mg showed dose-proportional PK parameters. The 1.0 mg strength was not dose-proportional compared to the other strengths.

PD: Zolpidem SL 3.5 mg resulted in statistically significant increases in daytime sedation for 20 min to 2.0 hr post-dose as measured by the CRT, DSST, and VAS. The 1.75 mg dose produced statistically significant daytime sedation from 20 min to 1.0 hr by the DSST, and from 20 min to 2.0 hr by the VAS. There was no significant difference in PD parameters between the 1.0 mg group and the placebo group. There is evidence of consistency between the PK and PD results.

The DSST scores suggest that by hour 2 post-dose the change in scores were ~1/3 of the maximum change (decreased ~ 4 points, compared to a 12 point decrease at 20 minutes post-dose). By hour 3, the DSST scores indicate that the scores for the zolpidem 3.5 mg group were above baseline, and similar to the placebo group changes. This trial design offers the best assessment available to us for evaluation of middle-of-the-night (hours 1 to 4) effects of the drug. Based on these findings, the risk appears to be relatively small if the 3.5 mg dose is taken when only 2.5 hours or less of bedtime remain.

Study ZI-16 - Comparison of zolpidem SL 3.5 mg SL (dissolved) and p.o. (swallowed)
Study ZI-16 was a single center, double-blind, double-dummy, single-dose, randomized, three-period, six-sequence, crossover PD study in 30 healthy volunteers. The primary objective was evaluation of the PD effects, assessed by DSST, of a single oral dose of 3.5 mg zolpidem tartrate immediately swallowed (p.o.) or sublingual (SL, dissolved in the mouth as instructed) compared to placebo.
The 3 treatments (with 5 – 7 day washouts) included:

Treatment A = 3.5 mg zolpidem tartrate p.o. followed by placebo SL
Treatment B = placebo p.o. followed by 3.5 mg zolpidem tartrate SL
Treatment C = placebo p.o. followed by placebo SL

DSST measurements were performed pre-dose, at 10, 20, and 40 minutes, and 1, 3, 4, and 5 hours post-dose. Blood samples for plasma zolpidem analysis (PK) were obtained pre-dose, at 1, 3, 4, and 5 hours post-dose.

The change from baseline in the DSST scores effected by 3.5 mg zolpidem tartrate SL dissolution or immediately swallowed (p.o.), compared to placebo is represented in Table 4.

Table 4. Pharmacodynamic Effect Areas for DSST Score (Change Over Baseline)

Assessment Time	**Mean (SD)**			**p-value**	
	zolpidem p.o. 3.5 mg (A)	**zolpidem SL 3.5 mg (B)**	**placebo (C)**	**A vs C**	**B vs C**
10 minutes	-0.7 (7.5)	-2.9 (7.6)	3.0 (5.1)	0.0158	0.0002
20 minutes	-8.0 (9.1)	-9.5 (9.5)	0.7 (7.1)	<0.0001	<0.0001
40 minutes	-5.0 (10.0)	-6.7 (8.5)	2.3 (7.4)	<0.0001	<0.0001
1 hour	-4.3 (10.8)	-6.8 (8.4)	2.4 (6.1)	0.0002	<0.0001
3 hours	-2.4 (7.4)	-2.1 (8.0)	0.2 (6.5)	0.1721	0.2270
4 hours	2.3 (6.7)	0.8 (7.0)	4.6 (6.0)	0.1386	0.0177
5 hours	1.7 (5.3)	1.8 (8.8)	1.1 (6.5)	0.192	0.7070

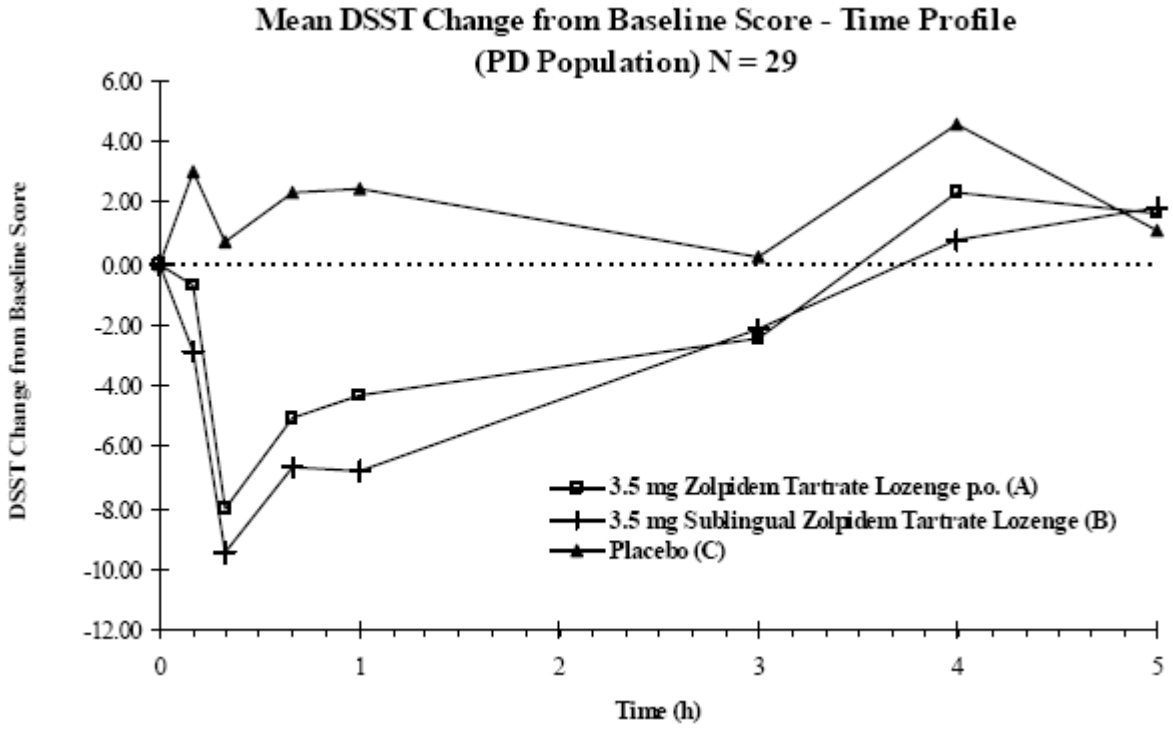
Source: Modified from Clinical Study ZI-16, Section 11.4.2

Differences between the sublingual and swallowed tablets did not reach statistical significance at any time point when compared to each other. Comparison of the

swallowed 3.5 mg dose to placebo showed statistical significance only at 20 min. and 40 min., while the 3.5 mg SL dose comparison to placebo reached statistical significance from 10 min. to 1 hour.

Fig. 5 shows changes over baseline in DSST scores for the three treatments. The oral and sublingual formulations are similar in responses compared to the placebo.

Fig. 5. Mean changes over baseline in DSST score – Study ZI-16



Source: Clinical Study ZI-16, Section 14

Safety:
One subject was discontinued due to adverse event (AE) reportedly not related to treatment. Other AEs included: 2 subjects (6.7%) reported blurred vision (both on 3.5 mg po), 1 subject reported a contusion (on 3.5 mg SL). Dizziness was reported by one subject in each of the 3 groups. Overall, 12 subjects (40.0%) experienced at least one treatment-emergent AE during the study. Sedation was the most frequently reported AE. The breakdown by treatment group is: 4 subjects (13.8%) of both the zolpidem p.o. and SL groups had complaints of AEs, compared to 5 subjects (16.7%) in the placebo group.

Conclusions and Comments:
The trial did not evaluate PK data. DSST change from baseline was statistically significant at 20 min., 40 min. and 1 hour for both the swallowed and sublingual doses of zolpidem 3.5 mg. The change in scores for the sublingual dose was reached significance by 10 minutes, so was faster in

effecting change than the swallowed tablet. The largest change in DSST score is noted in the measurement at 20 minutes for both the sublingual and swallowed routes of administration.

The shift in the scores of the placebo group at 20 minutes, and at 4 hours, complicate the data interpretation. Although not reaching statistical significance, the measurement at hour 3 post-dose does show that the zolpidem groups had not yet returned to baseline, but was decreased from baseline by only < 1/4 of the maximum change in score (at 20 minutes). DSST scores had returned to baseline (actually slightly higher) by the hour 4 measurements, but were still less than the mean placebo group score which had increased from baseline. The PD changes are paralleled in the PK (AUC) data.

The PD changes in the DSST scores in this trial suggest a slightly longer sedative effect since scores were still below baseline at hour 3, although above baseline by hour 4. The variability of the placebo scores are a confounding factor, and unfortunately, there is no testing data available for the periods between hour 1 and hour 3, or between hour 3 and hour 4. The trial sustains the sponsor's assertion that the sedative effects have dissipated by 4 hours post-dose, but the trial did not add substantially to the knowledge of what changes are occurring between hour 1 and hour 4 post-dose.

Conclusions and Comments:

PK/PD trials reviewed in this section were primarily designed to compare oral and sublingual formulations of zolpidem, and determine the effective dosage strengths. The pharmacodynamic assessments were limited to short-attention, simple tests. The PK conclusions will be included in the next section. (Section 4.4.3).

On the PD parameters, the 3.5 mg and 1.75 mg formulations showed maximum change at 20 minutes post-dose, and a return to baseline by hour 4 testing. The hour 1 to hour 4 test results would reflect the experience of a patient that used the drug with less than 4 hours of remaining sleep time. The trials were not specifically designed to investigate that time span and focused on the early (10 min. to 1 hour) and the end-point (hour 4) assessment. DSST scores for the zolpidem 3.5 mg were decreased compared to the placebo group (reaching statistical significant from 10 minutes through 1 hour post-dose) in all testing. By hour 3, PD results do not show a statistically significant difference from placebo, and are close to baseline (and above in some measurements). At hour 4, PD measures are back to baseline (slightly above) but still slightly below the measures for the placebo group (due to performance improvement with repetition). The PD data substantiates the sponsor's claims for rapid onset and return to baseline by hour 4.

Comparing the PD data for the sublingual (SL) rather than p.o. (swallowed) administration of zolpidem 3.5 mg tablets indicates that the sublingual administration may have slightly more rapid onset, and slightly larger PD effect from 20 minutes to 1 hour post-dose, but effects by hour 3 are nearly the same.

Safety data from the above trials is included in the combined safety review, but included here as well since the AEs could be linked to both PK and PD values for the individual subjects. Comparison of AEs for the swallowed and sublingually-dissolved tablets of zolpidem tartrate lozenge 3.5 mg showed no significant differences in regarding the number and pattern of AEs. Swallowing the zolpidem 3.5 mg SL rather than allowing it to dissolve appears to pose no safety risk. There were no significant safety issues during the course of the trials. The incidence of AEs was similar between the zolpidem 3.5 mg SL and the zolpidem tartrate 10 mg oral tablet (Ambien), but it was slightly higher than with the oral zolpidem tartrate 3.5 mg tablet, or with the placebo (Study ZI-17). Increased reports of headache (by 3 subjects) was the main reporting difference with the zolpidem SL.

4.4.3 Pharmacokinetics

No mechanism of action studies were required or conducted due to the use of Ambien as the approved reference drug. The clinical development program included four single-dose bioavailability trials which were not included in the clinical review:

Study ZI-04-001-001 – evaluation of different swallowing times for powdered sublingual zolpidem 10 mg (8 healthy subjects)

Study ZI-04-002-002 and ZI-04-003-003 – evaluation of 10 minute and 5 minute dissolution time, respectively, of 10 mg tablets of zolpidem SL to oral Ambien® (8 healthy subjects each)

Study ZI-04-007-007 - comparison of zolpidem 10 mg SL to 10 mg oral Ambien® (9 healthy subjects).

The trials evaluated the PK effects of the prototype formulations for in-mouth disintegration time, and in-mouth disintegration versus swallowing of the tablet. Based on the trial results, the sublingual disintegration time is 2 -3 minutes, and absorption slightly shorter than with swallowing. These trials were not included in this review since they used only the 10 mg formulations, but were included in the review by Clinical Pharmacology which will be filed separately.

A bioequivalence trial, Study ZI-13, an open-label, single-dose, 2-sequence crossover study of 36 healthy subjects demonstrated the bioequivalence of IND formulation to the proposed commercial formulation (3.5 mg dose strengths for each). Differences between the formulations were not statistically significant. The time to reach maximum concentration was 56 minutes for the commercial formulation, and 44 minutes for the IND formulation. The IND formulation was used in one of the two clinical trials (the PSG-monitored Study ZI-06-010). It is difficult to

estimate if a difference of ~12 minutes in the two formulations could have an effect on the endpoints for the pivotal clinical trials since the comparison of objective (PSG) and subjective data collection is involved. T_{max} ranged from 20 to 120 minutes for both formulations. Overall drug concentration appears to be very similar for the two formulations.

Based on the ZI-13 bioequivalence data, subsequent Studies ZI-14, ZI-15, ZI-16, and ZI-17, and one of the two pivotal trials, Study ZI-12, utilized the proposed commercial formulation rather than the IND formulation. Study ZI-006-010, the other pivotal clinical trial, conducted earlier, relied on the IND formulation.

Study ZI-14 – Comparison of elderly to non-elderly cohorts, and of 2 strengths zolpidem SL

Study ZI-14 is an open-label, single-dose, 2-sequence daytime PK trial that examined the pharmacokinetics of the 1.75 mg and 3.5 mg zolpidem SL in a crossover trial of 24 elderly subjects, and a parallel trial of zolpidem SL 3.5 mg in the 24 elderly subjects compared to 24 non-elderly subjects. The trial was reviewed because although it is only a PK trial, it is the only trial that represents use of the drug in an elderly cohort. The trial was designed to establish a PK bridge for use of the zolpidem 1.75 mg in the elderly. The Agency agreed in pre-NDA meetings to allow labeling for use in the elderly if PK data was supplied to demonstrate that the PK bioavailability measurements of zolpidem 1.75 mg in the healthy elderly fell between measurements of zolpidem 3.5 mg in adult volunteers.

The trial showed dose-proportional responses comparing the 1.75 mg to the 3.5 mg doses in the crossover elderly cohorts, and also in the 1.75 mg elderly cohort compared to the 3.5 mg non-elderly cohort early PK parameters. In the latter trial, bioavailability of the 1.75 mg dose in the elderly cohort was less than in the 3.5 mg dose for the non-elderly cohort (by confidence interval analysis for AUC and C_{max}.(Table 5) Comparison of the PK data for the elderly and non-elderly cohorts is represented in Fig. 7.

Table 5. Summary of PK Results for 2 Dose Strengths – Elderly Cohort, Study ZI-14

		Zolpidem SL 1.75 mg [a] Elderly Cohort, n=22		**zolpidem SL 3.5 mg [a] Elderly Cohort, n=22**		**zolpidem SL 3.5 mg Non-Elderly Cohort, n=22**	
Parameters		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
AUC_{0-t}	(ng·h/mL)	164.7	320.1	320.1	151.8	242.4	101.1
AUC_{0-inf}	(ng·h/mL)	181.4	352.4	352.4	187.9	263.0	121.0
AUC_{0-4h}	(ng·h/mL)	100.6	194.2	194.2	72.5	149.7	44.4
$AUC_{t/inf}$	(%)	92.2	93.0	93.0	5.1	93.6	4.1
$AUC_{0-[25\ ng/mL]}$	(ng·h/mL)	3.8	3.7	3.7	2.2	4.3	2.6
C_{max}	(ng/mL)	41.0	83.1	83.1	25.0	61.9	15.8
T_{max} (Mean)	(h)	0.60	0.6	0.58	0.4	0.76	0.4
T_{max} (Median)	(h)	0.42[b]	0.5[b]	0.46[b]	0.3[c]	0.67a	0.2b
$T_{1/2max}$	(h)	0.20	0.2	0.25	0.1	0.36	0.2
$T_{½\ el}$	(h)	2.8	2.7	2.7	0.9	2.6	0.8

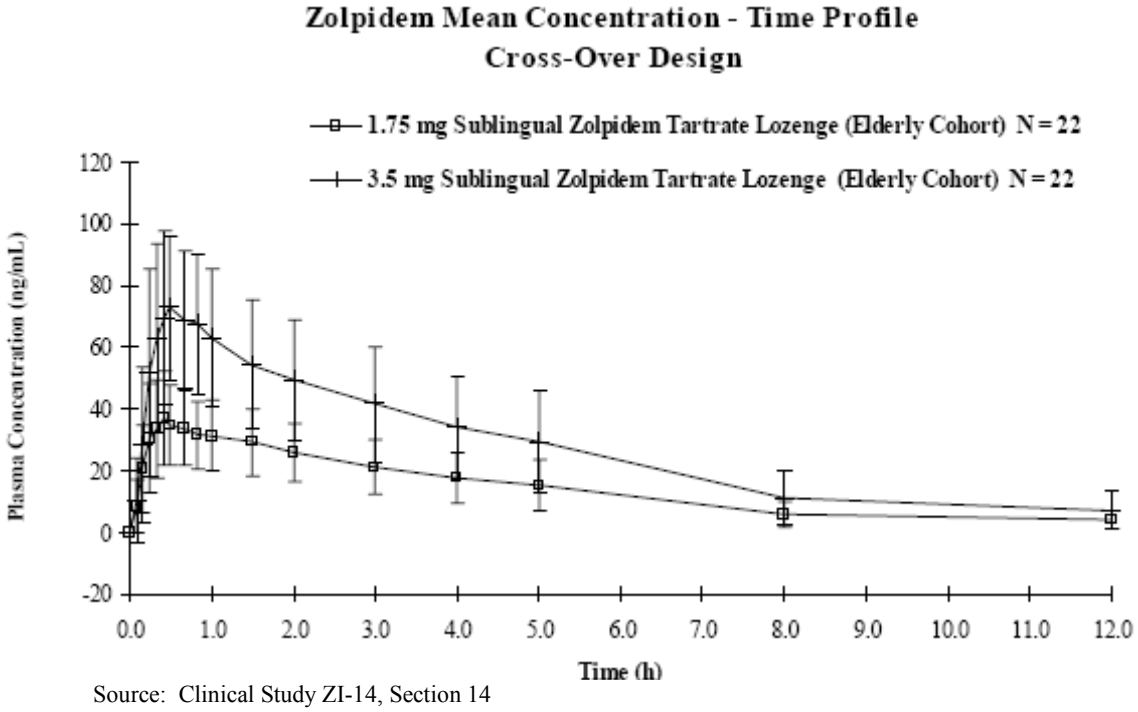
AUC0-inf = Area under the concentration-time curve from time zero to infinity; AUC0-t = Area under the concentration time curve from time zero to time of last non-zero; AUC0-4h = Area under the concentration-time curve from time zero to time 0 to 4h; AUC0-[25 ng/mL] = Area under the concentration-time curve from time 0 to the first concentration above 25 ng/mL; UCt/inf = Ratio of AUC0-t to AUC0-inf ; Cmax = Maximum observed concentration; PK = Pharmacokinetic; T1/2 el = Elimination half-life; Tmax = Time of observed Cmax; T½max = Estimated time to observe half Cmax; T[25 ng/mL] = Time of the first concentration above 25 ng/mL.

[a]Data from all subjects who completed both periods were included in this PK and statistical analysis.

[b]Medians are presented. [c]Interquartile ranges are presented

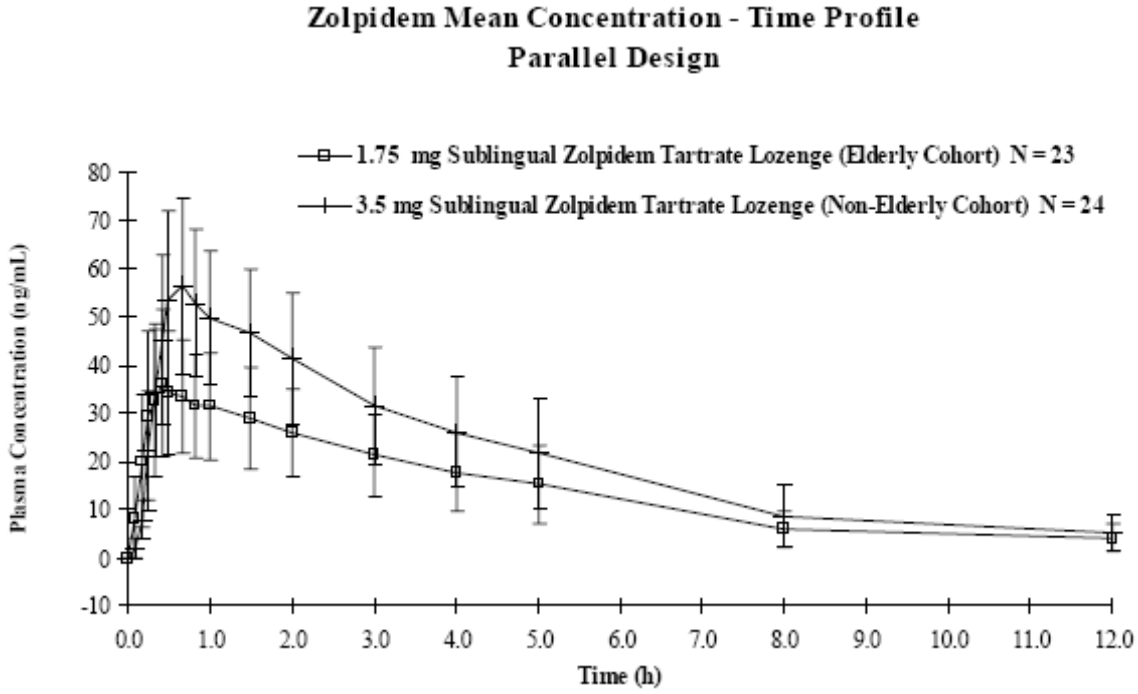
Source: modified from Clinical Study ZI-14, Section 11.4.2

Fig. 6. Pharmacokinetic Results for 2 Dose Strengths – Elderly Cohorts – Study ZI-14



Source: Clinical Study ZI-14, Section 14

Fig. 7. Pharmacokinetic Results for 2 Dose Strengths – Elderly and Non-Elderly Cohorts



Source Clinical Study ZI-14, Section 14

The comparison of the 3.5 mg and 1.75 mg formulations in the elderly shows a consistent dose-proportional relationship. The PK values for AUC, Cmax, and Tmax for the adult subjects (3.5 mg) fall between the PK values for the elderly subjects receiving 1.75 mg and 3.5 mg zolpidem SL. The trial fulfills the agreement with the Agency and allows labeling recommendations for the 1.75 mg dose for the elderly.

Although rather difficult to distinguish in figure above, when the first half-hour interval post-dose is analyzed, the elderly cohort (1.75 mg) shows a slightly higher plasma concentration, but by 20 minutes post-dose, the non-elderly cohort (3.5 mg) surpasses them for the remainder of the C_{max} assessments.

The trials reviewed showed 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 PK or PD parameters. The PK comparison to the dose-adjusted Ambien 10 mg gave similar results on all PK measures.

The PK data are acceptable. Although no PD data are available, the safety review did not raise concerns for the use of the drug at the recommended 1.75 mg strength for elderly patients.

The safety data for Study ZI-14 is included in the pooled safety data, and discussed separately in Section 7.4.1, Common Adverse Events).

Study ZI-15 – Comparison of zolpidem SL 3.5 mg fed and fasting, and to Ambien® 10 mg

Study ZI-15, a single-dose PK, open-label, 3-period, 6-sequence trial in 36 healthy subjects, compared the effect of food on zolpidem SL 3.5 mg vs. oral Ambien® 10 mg. This was the only trial that did not test all formulations or dosages under fasting conditions. Administration of the zolpidem SL 3.5 mg 30 minutes after a standard high-fat breakfast decreased C_{max} by ~ 38%, and AUC_{0-t} was decreased ~ 20% by food effect. T_{max} was increased from 1 hour (fasted) to 3 hours (fed).

The trial also compared zolpidem SL 3.5 mg (fasted) to Ambien 10 mg (fasted) for bioavailability. The AUC_{0-t} and C_{max} of the zolpidem SL were ~38% and 39% respectively of the oral Ambien® 10 mg. The C_{max} of the zolpidem SL (fed and fasted) was higher during the first 15 minutes after administration than the C_{max} of the Ambien® 10 mg.

Comparing the early plasma concentrations (fasted) of zolpidem SL 3.5 mg to Ambien® 10 mg at 15 minutes post-dose shows 19.9 and 12.5 ng/mL, respectively, as shown in Table 6. But already at 20 minutes post-dose, the Ambien® has a higher plasma concentration. The Cmax is 57.2 and 146.6 for the zolpidem SL 3.5 mg and Ambien® 10 mg, respectively.

The AUC for zolpidem SL 3.5 mg is larger than that of Ambien® 10 mg at 15 and 20 minutes post-dose, but by 1 hour post-dose, the zolpidem SL 3.5 AUC is only ~half of the Ambien® AUC (32.6 and 67.3 ng·h/mL , respectively).

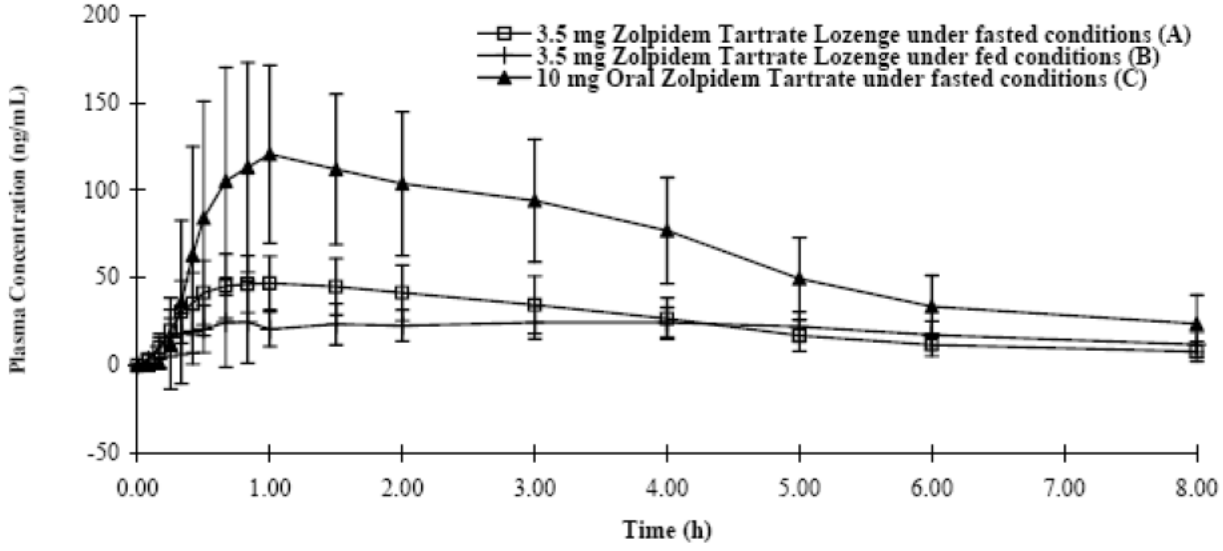
Table 6. **Pharmacokinetic Results (Fasted) – zolpidem SL 3.5 mg and Ambien® 10 mg – ZI-15**

		Zolpidem SL 3.5 mg Fasted, n=33 (A)			Ambien® 10 mg Fasted, n=33 (C)		
Parameters		**Mean**	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC_{0-t}	(ng·h/mL)	201.4	74.3	36.9	525.3	188.1	35.8
AUC_{0-inf}	(ng·h/mL)	231.4	100.1	43.2	620.7	281.8	45.4
AUC_{0-4h}	(ng·h/mL)	145.5	48.4	33.2	362.8	124.6	34.3
AUCt/inf	(%)	89.1	6.2	6.9	87.3	7.5	8.6
$AUC_{0-15\ min}$ a	(ng·h/mL)	1.9	1.0	54.6	0.6	1.3	200.4
$AUC_{0-20\ min}$ a	(ng·h/mL)	4.0	2.0	50.8	2.7	4.2	156.2
$AUC_{0-[25\ ng/mL]}$	(ng·h/mL)	6.8	7.3	107.3	7.5	14.8	197.3
AUC_{0-1h}	(ng·h/mL)	32.6	12.2	37.5	67.3	38.6	57.3
$AUC_{0-[Tmax]}$	(ng·h/mL)	41.6	42.0	101.0	73.3	69.4	94.8
C15 min a	(ng/mL)	19.8	11.9	59.9	12.5	26.0	207.8
C20 min a	(ng/mL)	30.5	17.9	58.9	36.1	46.5	128.8
Cmax	(ng/mL)	57.2	15.9	27.8	146.6	50.9	34.7
Tmax (Mean)	(h)	1.2	0.8	70.0	1.2	0.9	73.2
Tmax (Median)b	(h)	1.00	0.8	N/AP	0.83	0.6	N/AP
$T_{1/2max}$ a	(h)	0.45	0.43	96.4	0.58	0.4	71.6
$T_{[25\ ng/mL]}$	(h)	0.52	0.5	98.7	0.56	0.5	91.2
Kel	(h-1)	0.33	0.1	26.2	0.32	0.1	25.8
T½ el	(h)	2.2	0.6	27.1	2.3	0.7	31.8

AUC0-inf = Area under the concentration-time curve from time zero to infinity; AUC0-t = Area under the concentration-time curve from time zero to time of last non-zero; AUC0-4h = Area under the concentration-time curve from time zero to time 0 to 4h; AUCt/inf = Ratio of AUC0-t to AUC0-inf ; AUC0-15 min = Area under the concentration-time curve from time zero to time 0 to 15 minutes postdose; AUC0-20 min = Area under the concentration-time curve from time zero to time 0 to 20 minutes post-dose; AUC0-1h = Area under the concentration-time curve from time zero to time 0 to 1 hour post-dose; AUC0-[Tmax] = Area under the concentration-time curve from time zero to time 0 to the time of observed Cmax; AUC0-[25 ng/mL] = Area under the concentration-time curve from time 0 to the first concentration above 25 ng/mL; C15 min = Observed concentration at 15 minutes post-dose; C20 min = Observed concentration at 20 minutes post-dose; Cmax = Maximum observed concentration; Tmax = Time of observed Cmax; T½max = Estimated time to observe half Cmax; T[25 ng/mL] = Time of the first concentration above 25 ng/mL; Kel = Elimination rate constant; T1/2 el = Elimination half-life; N/AP = Calculation not applicable.
a For these parameters, N = 32 for Treatment A. b Medians and interquartile ranges are presented. c For these parameters, N = 23 for Treatment B. Source: Clinical Study ZI-12 Section 11.4.2

Comparison of the mean plasma concentrations for zolpidem 3.5 mg (both fasted and fed) and Ambien® 10 mg (fasted) is represented in Fig. 8.

Fig. 8. Zolpidem Mean Concentration – Time Profile, n=33, Study ZI-15



Source: Clinical Study ZI-15, Section 14.2.2

Conclusions and Comments:
The food effect on the zolpidem SL 3.5 mg showed a decrease in Cmax of ~ 38%, and AUC_{0-t} (~19%) and delayed Tmax from 1.2 hours (fasted) to ~ 2.7 hours (fed). Plasma concentrations during the first 15 minutes for the zolpidem fed and fasted were greater than those of the reference drug, Ambien® 10 mg. The sponsor attributed this to sublingual absorption which should be relatively unaffected by food effect. The trial indicates that the sublingual tablet reaches a higher AUC at 15 and 20 minutes, and a higher plasma concentration only at 15 minutes post-dose than Ambien® 10 mg. (b) (4) The Clinical Pharmacology review notes that by the reviewer's reanalysis of the bioequivalence between zolpidem SL and Ambien (dose normalized) under fasted conditions, the 90% confidence interval (CI) levels for upper boundary of Cmax was above 125% limit.

The trials reviewed showed no statistically significant differences between 3.5 mg zolpidem sublingual and 3.5 mg zolpidem p.o. (swallowed).

Except for the first 15 to 20 minutes, the Cmax and AUC of zolpidem SL 3.5 mg are below that of the reference listed drug, Ambien® 10 mg, and fulfill the FDA requirement for a comparative bioavailability study.

As indicated in the PK trials, although the DSST scores (PD scores) return to baseline by about hour 3 post-dose, the PK parameters remain elevated (see Fig. 1, Fig. 6, Fig. 7, and Fig. 8). The therapeutic serum levels for Ambien® are 29 to 272 ng/mL; presumably the concentration at which the drug is effective at sedation. To determine when zolpidem SL 3.5 mg would fall below the 29 ng/mL, Clinical Pharmacology was consulted and determined that Ambien® 10 mg fell below that level at 5.5 hours, and zolpidem 3.5 mg/mL fell below that level at …….. (based

on estimates from Study ZI-15). Most of the trials suggest that the levels for zolpidem SL 3.5 mg have nearly fallen below that therapeutic level by hour 3 post-dose.

Zolpidem SL 3.5 mg and 1.75 mg showed dose-proportional PK findings under fasting conditions in elderly cohorts. Mean exposure (AUC and Cmax) to zolpidem from 3.5 mg sublingual zolpidem was approximately 34% higher in elderly subjects compared to younger adults.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In the development of the low-dose zolpidem tartrate sub-lingual (SL) tablets, Transcept conducted the trials listed below: (See Appendix Table 1).

Pharmacokinetic/Pharmacodynamic Studies

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

ZI-13 – "A Randomized, Open-label, Two-Period, Two-Sequence Crossover Study to Evaluate the Bioequivalence of Two Different Formulations of ST Zolpidem in Healthy Adult Subjects"

ZI-14 – "A Randomized, Open-Label, Two-Period, Two-Sequence, Crossover Study to Evaluate the Pharmacokinetics of Sublingual Zolpidem Tartrate Lozenge in Healthy Elderly Subjects as Compared to Healthy Non-Elderly Subjects"

ZI-15 – "A Study to Assess the Comparative Single-Dose Pharmacokinetics of 3.5 mg Sublingual Zolpidem Tartrate Lozenges (Intermezzo®) in the Fed and Fasted State, and 10 mg Oral Zolpidem Tartrate (Ambien®) in the Fasted State in Healthy Adult Subjects"

ZI-16 – "A Study to Evaluate the PD Effects of Orally Administered Zolpidem Tartrate Lozenges (Intermezzo® 3.5 mg) as Assessed by the Digit Symbol Substitution Test"

ZI-17 – "A Two Part Study in Healthy Adult Volunteers to Assess the Comparative Early PK Parameters and PD Effects of the Sublingual Zolpidem Tartrate 3.5 mg Lozenge and the Oral Zolpidem Tartrate 3.5 mg Tablet; and to Describe the PK Dose Proportionality Between the Oral Zolpidem Tartrate 10 mg (Ambien®) and 3.5 mg Tablets"

Efficacy Studies

ZI-06-010 – "A Randomized, Double-blind, Daytime, 4-way Crossover Study to Evaluate the Pharmacokinetics, Dose Proportionality, Pharmacodynamics, Safety and Tolerability of Three Doses of Sublingual Zolpidem Tartrate Lozenges compared to Placebo in Normal Healthy Volunteers"

ZI-12 – "A Randomized, Double-blind, Placebo-controlled, Crossover Study of the Efficacy and Safety of TransOral Zolpidem in Adult Patients with Insomnia Characterized by Difficulty Returning to Sleep after Middle-of-the-Night (MOTN) Awakening"
The pivotal Phase 3 trials, ZI-06-010, a cross-over polysomnography (PSG) -monitored sleep lab crossover trial enrolled 82 subjects, and ZI-12, an outpatient 2-week trial, enrolled 294 subjects for a total of 376 subjects.

The combined trials (all phases) included a total of 618 subjects with at least one exposure to the trial drug.

5.2 Review Strategy

The efficacy review focused on the two pivotal trials, ZI-06-010, and ZI-12 submitted in support of this application, but also included review of all the pharmacodynamic (PD)/pharmacokinetic (PK) trials for specific topics of review interest. The safety review included submitted data from all trials in Phase 1, Phase 2 and Phase 3 that included use of the zolpidem 3.5 mg dose strength. Also included in the safety review was information from the Annual Reports for the past 2 years for the zolpidem tartrate products.

5.3 Discussion of Individual Studies/Clinical Trials

The development program for zolpidem SL 3.5 mg and 1.75 mg included the initial tolerability, dose-ranging, and BE studies ZI-14, ZI-15, and ZI-040007-007.

Reports of Human Pharmacodynamic (PD) Studies: PD and PK/PD Study Reports included ZI-16, ZI-05-009, and ZI-17.

The efficacy trials are the two pivotal Phase 3 trials:

- ZI-06-010: an in-clinic, multi-center, placebo-controlled, PSG-monitored cross-over trial of 2 zolpidem SL dose strengths (3.5 mg and 1.75 mg) in adult subjects with MOTN insomnia; duration of active treatment was three 2-night periods with wash-out periods between.

- ZI-12: A outpatient (at-home), parallel group trial assessing 3.5 mg zolpidem SL vs. placebo in adult subjects with MOTN insomnia; duration of active treatment was 4 weeks (28 nights) of "as needed" self-administration.

6 Review of Efficacy

Efficacy Summary

Study ZI-06-010

The PSG-monitored sleep lab cross-over trial averaged the 2 nights of each treatment period for the PSG data, and also used a questionnaire, so both objective and subjective data collection was done for 2 dose strengths (zolpidem 3.5 mg and 1.75 mg) compared to placebo. By previous agreement with the Agency, adjusted LS means were used for the statistical analysis of both pivotal trials.

The primary endpoint was change in Latency to Persistent Sleep following middle-of the night awakening (LPS_{MOTN}) for zolpidem SL 3.5 mg compared to placebo. The trial showed dose-related decreases that reached statistical significance favoring the 3.5 mg and 1.75 mg zolpidem groups (change for the lower dose was a secondary endpoint). Actual time for resumption of sleep is rather difficult to interpret since the study design called for MOTN awakening followed by 30 minutes awake time. Measurements for return to sleep are taken from the second lights out. At baseline, mean LPS (SEM) was 50 minutes. The post-treatment mean LPS (LS mean) was 9.7 minute, 16.9 minutes and 28.1 minutes for the zolpidem 3.5 mg, 1.75 mg., and placebo groups, respectively ($p<0.001$ for both zolpidem doses compared to placebo and to each other). Comparison of the zolpidem doses to placebo show a LS mean decrease of ~ 18 minutes for the 3.5 mg dose, and 11 minutes for the 1.75 dose of zolpidem. The change was consistent comparing Day 1 to Day 2 of each treatment. When evaluating the efficacy of the LPS_{MOTN} in a sub-group analysis of subjects with more prolonged MOTN insomnia at baseline ($\geq$ 60 min.), the 3.5 mg dose was more effective ($p<0.001$, zolpidem 1.75 mg $p = 0.003$).

On the secondary endpoints, TST_{MOTN} (174 min. at baseline) increased for both zolpidem groups compared to placebo, an increase of ~ 26 minutes for the zolpidem 3.5 mg group and 15 minutes for the 1.75 mg group (both with $p<0.001$ compared to placebo, and 0.005 compared to each other). The averaged LS mean for TST_{MOTN} was 209 min., 198 min. and 183 min. for zolpidem 3.5 mg, 1.75 mg and placebo respectively, baseline was 174 min. (SEM). Again evaluating the efficacy of the LPS_{MOTN} in a sub-group with prolonged MOTN insomnia at baseline (baseline TST_{MOTN} of 150 minutes), the 3.5 mg dose was more effective increasing TST 28 minutes ($p<0.001$), and 13 min. for 1.75 mg ($p = 0.027$), compared to placebo. The morning questionnaire responses to TST_{MOTN} showed a nearly identical pattern.

Sleep efficiency (by PSG analysis) for the zolpidem groups improved compared to placebo ($p<0.001$ both doses). And the subjective ratings of sleep onset latency (sSOL) and Sleep Quality (sSQ) both showed improvement for the zolpidem groups compared to placebo (both doses with $p<0.001$ for the former, and $p=0.111$ for 1.75 mg dose).

It is note-worthy that neither zolpidem SL 3.5 mg or 1.75 mg doses showed a significant decrease on WASO or NAW. The sponsor had designated these as exploratory endpoints.

The trial met its primary LPS_{MOTN} endpoint for the zolpidem SL 3.5 mg dose, and also for the 1.75 mg dose by decrease of ~18 min. and ~11 min. respectively which is probably enough to be significant to a patient with MOTN insomnia. Interpretation is clouded by the requirement that subjects were required to stay awake for 30 minute post-dose, so the time changes reflect time from second "lights out" rather than post-dose time which makes it difficult to translate the exact time change to expectations for use in the home setting. Despite those reservations, there was a dose-related decrease in LPS_{MOTN}, and there was reinforcement of results with the assessment of the secondary endpoints. The subjective reports on the morning questionnaire parallel the PSG findings.

Study ZI-12

All measurements for the outpatient trial were based on the nights for which the assigned study medication (zolpidem 3.5 mg or placebo) was self-administered (after approval obtained), and used the average of the 4 weeks of treatment, as well as individual weeks. All measurements are based on subjective data.

At baseline, the primary endpoint, subjective Latency to Sleep Onset after middle-of the night awakening ($sLSO_{MOTN}$) was 68 minutes for the zolpidem group, and 69 min. for the placebo group. The post-treatment average showed $sLSO_{MOTN}$ of 38 min. for the zolpidem group (a 30 minute reduction) compared to 56 min. for the placebo group (a 13 min. reduction). That gives a treatment-attributable decrease in return to sleep of ~ 17 minutes. The difference in the primary endpoint reached statistical significance ($p<0.0001$) favoring the zolpidem-treated group.

The first secondary endpoint (of the hierarchy) was subjective Total Sleep Time following middle-of-the-night-awakening ($sTST_{MOTN}$). It was directionally positive (mainly in the first week), but not statistically significant for the zolpidem group, possibly because of baseline imbalance between the groups. Under the hierarchical approach to analysis of the secondary end points as defined in the SAP, the other secondary end points, $sNAW_{MOTN}$ and $sWASO_{MOTN}$, are considered exploratory. The 3.5 mg zolpidem tartrate sublingual lozenge showed statistically significant effects on $sNAW_{MOTN}$ and $sWASO_{MOTN}$ on the 4-week treatment average, and on Weeks 1,2 and 3 (not Week 4). An exploratory endpoint of improvement in sleep quality on nights study medication was taken showed significant difference favoring the zolpidem group for the 4-week mean, and each of the weeks.

This trial also met its primary endpoint $sLSO_{MOTN}$ with a decrease of ~18 minutes in time to return to sleep for the zolpidem group compared to placebo group. Although based on subjective reports, the time decrease is nearly the same as the findings for the 3.5 mg dose in ZI-06-010 which reinforces the result reliability for both trials. The lack of statistical significance in the primary secondary endpoint (an increase in TST of 9 minutes for zolpidem compared to placebo) caused all other endpoints to be regarded as exploratory for this review. However, the zolpidem group results did show improvement on most of the endpoints, including sNAW and sWASO.

Overall both trials could be considered to have adequately demonstrated efficacy for zolpidem SL 3.5 mg. The 1.75 mg dose strength also appears to have demonstrated efficacy, although not consistently at a statistically significant level. Since the efficacy trial enrolled only non-elderly subjects, and the 1.75 mg dose is recommended for elderly patients, the earlier PK trials information combined with the ZI-06-010 data suggest that the 1.75 mg dose should be appropriate for the older patients.

6.1 Indication

The indication for both of the Phase 3 trials is the treatment of insomnia characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakening.

6.1.1 Methods

The sponsor submitted two Phase 3 clinical trials for efficacy.

Study ZI-06-010
Study ZI-06-010 (IND 69,209) was a multi-center (5 US sites), randomized, double-blind, placebo-controlled, 3-period crossover (2 successive nights each treatment period), polysomnography (PSG) sleep lab trial evaluating 2 zolpidem SL dosage strengths (3.5 mg and 1.75 mg), compared to placebo.

The study duration was 6 nights total (with subjects randomized to zolpidem tartrate lozenge 3.5 mg for 2 nights, zolpidem tartrate lozenge 1.75 mg for 2 nights, and placebo for 2 nights). Treatment periods were separated by a 5- to 12-day washout interval.

Initial screening (within 28 days of randomization) included physical examination, medical and sleep histories, 12-lead electrocardiogram (ECG), clinical laboratory assessments, and completion of a 10-day sleep diary. Patients also completed PSG screening and baseline recording for 2 consecutive nights in which they received single-blind placebo after a scheduled MOTN awakening (see below). Following the screening phase, subjects were randomized 1:1:1for the 2 drug strengths and placebo groups.

During the active trial phase, the schedule established during the screening nights was used: lights out (at 22:45 hour $\pm$ 30 minutes), then subjects awakened 4 hours later, administered the study drug (for 2 consecutive nights), completed a MOTN Awakening Questionnaire, and were kept awake for 30 minutes before returning to bed for 4 more hours sleep. PSG measurements were recorded for 8 hours on each of the 6 nights (4 hours before the scheduled MOTN awakening, and 4 hours after the MOTN 30-minute awake period). At the end of the second 4-hour PSG sleeping period, subjects were awakened. After a 30 minute interval (for dressing and toileting), subjects completed a Treatment Morning Sleep Questionnaire (TMSQ) followed by the Digit Symbol Substitution Test (DSST) and Visual Analog Scale for sedation/alertness

(VAS), and oral cavity check was done. Subjects were allowed to leave after they performed a negative heel-to-toe gait test.

Study ZI-12
Study ZI-12 was a 4-week (of active treatment), multi-center, randomized, double-blind, placebo-controlled, parallel group, outpatient trial . Study drug (zolpidem SL 3.5 mg or placebo) was used as-needed (prn) only on nights that middle-of-the night insomnia occurred, and permission was received for use of the assigned study drug.

During the 2-week screening period, subjects were instructed to call the Interactive Voice Recording System (IVRS) after waking up in the night. The subjects had to answer questions regarding whether they had been awake for at least 10 minutes and still had at least 4 hours remaining in bed. If these criteria were met, they were instructed to self-administer the placebo sublingual tablet return to sleep. Each morning (whether or not they had a middle-of-the-night awakening, or took medication), subjects called the IVRS and responded to questions concerning the previous night's sleep. Following successful completion of the 2-week screening period, subjects were randomized (1:1 ratio) to zolpidem SL 3.5 mg or to placebo.

Instructions for the 4-week active treatment period were essentially the same as the screening period. Subjects were instructed to call the IVRS when they had a middle-of-the-night awakening of $\geq$10 minutes, and had $\geq$4 hours time in bed remaining. The IVRS gave permission for self-administration of the assigned study drug only if these criteria were met. The active treatment period was 28 days. Enrolled subjects received a bottle of 15 sublingual tablets (zolpidem 3.5 mg or placebo) at Visit 2 (Randomization or Day 1 of treatment), and at Visit 3 (Day 14 of Treatment Period).

Fig. 9. Study design and schedule of assessments – Study ZI-12

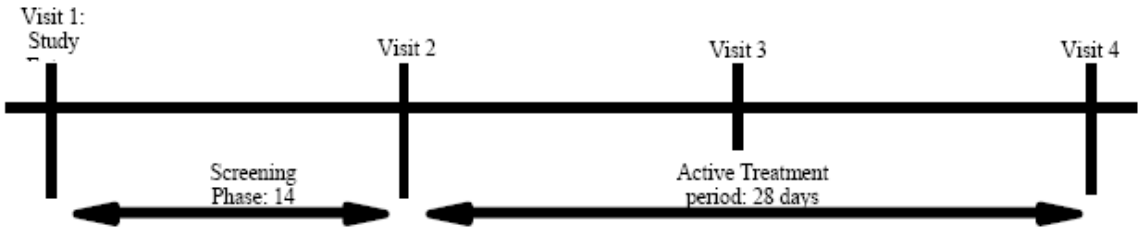


Table 7. Schedule of Assessments – Study ZI-12

Phone Screen	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Eligibility criteria initially screened by phone	Starting 2-Week Single-blind Screening Period Informed consent Perform study procedures Issue 2-week supply of placebo Use IVRS to collect sleep data each morning	Beginning of 4-Week Double-blind Treatment Period Perform study procedures Randomization Issue 2-week supply of study medication (3.5 mg zolpidem tartrate sublingual lozenge or placebo) Use IVRS to collect sleep data each morning	Interim visit—end of Week 2 Treatment Period Perform study procedures Issue 2-week supply of study medication Use IVRS to collect sleep data each morning	End of 4-Week Double-blind Treatment Period or early discontinuation Perform study procedures

6.1.2 Demographics

Study ZI-06-010
This trial recruited adult subjects with primary insomnia based upon DSM-IV and PSG criteria. Inclusion criteria:

- Male and female patients between the ages of 18–64 years with a body mass index (BMI) between 18 and 34, and an established diagnosis of insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TRTM) criteria
- History of MOTN awakenings for at least 4 weeks characterized by ≥ 3 nights per week with an awakening episode, and sleep onset latency (SOL) of ≥ 30 minutes per awakening
- Based on completion of at least 7 days of the 10-day Screening Morning Sleep Diary, patients must also have met the following criteria:
    - Self-reported ≥ 3 nights with a MOTN awakening
    - Self-reported SOL of ≥ 30 minutes on at least 3 awakenings
    - Stable bedtime pattern as defined by:
        - Usual bedtime between 2200 and 2400 hr inclusive, on all 7 days
        - Usual rise time between 0500 and 0800 inclusive, on at least 5 days (not varying by more than 2 hours on 5 of 7 days)
- During the 2-night PSG single-blind placebo screening phase, patients with a scheduled MOTN awakening followed by 30 minutes wake time on both nights had to have a mean latency to persistent sleep (LPSMOTN) ≥ 20 minutes and on neither night had a LPSMOTN <15 minutes following single-blind placebo treatment

Exclusion criteria for both trials was standard for insomnia studies, and also specified exclusion of any subject with consumption of more than 14 units of alcohol per week, and any subject who currently smoked more than 5 cigarettes or equivalent per day, or who was unable to abstain from smoking during a middle-of-the-night awakening.

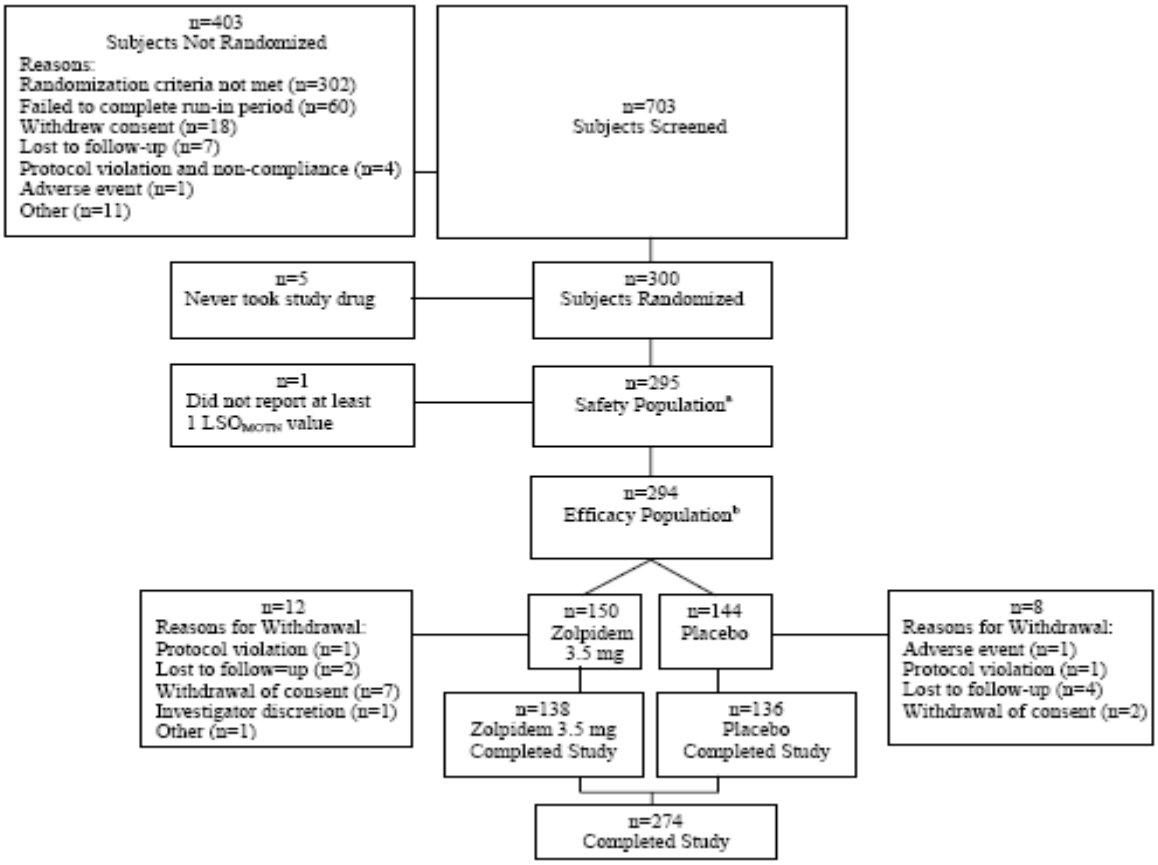
Study ZI-12
The majority of the inclusion criteria were the same as in Study ZI-06-010. The only variation was in the requirement that subjects have an insomnia history ≥3 months duration with TST of ≤6.5 hours (with time in bed of 7 to 9 hours). Inclusion criteria also included screening phase requirements of: compliance with the IVRS calling instructions, at least 1 MOTN awakening of ≥60 min. per week, and at least 2 further MOTN awakenings per week of ≥30 min. (with at least 4 hours sleep time remaining).

6.1.3 Subject Disposition

Study ZI-06-010 (PSG, cross-over study)
Conducted at 5 sleep lab sites in the US
Enrolled: 83, Received ≥ 1 dose: 82,
Completed: 80
Subject Composition: ages 19-64 years (mean 45.9 ±12 yrs), 58/82 (71%) female, Caucasian 42/82 (51%), Black 36/82 (44%), Hispanic 2/82 (2%), Asian/Pacific 2/82 (2%)
Number of nights with MOTN awakenings: mean 9.1 ±1.2, median 10.0, range 5, 10
All 82 patients were analyzed for safety and efficacy. Two patients were discontinued (one for withdrawal of consent, and one due to a family emergency).

Study ZI-12
Conducted at 25 sites (pooled regionally to 12 sites for statistical analysis) and included:
Screened: 703, Randomized: 300, Received ≥ 1 dose: 294 (150 on zolpidem SL 3.5 mg, 145 on placebo)
Completed: 274 (138 on zolpidem 3.5 mg, 136 on placebo)
Subject Composition: ages 18-64 years, median age 43 years, 68% were female, 64% were white, and 31% were black or African-American.
The reasons for exclusion are most succinctly summarized in the subject disposition chart (Fig. 10. Disposition of Subjects)

Fig. 10. Disposition of Subjects – Study ZI-12



[a]The safety population includes all randomized subjects who took at least 1 dose of study medication during the double-blind treatment phase of the study.
[b]The efficacy population includes all randomized subjects who took at least 1 dose of study medication and had at least 1 LSOMOTN value.
Source: Study ZI-12, Section 10.1

The "at home" Study ZI-12 provides the best insight into the baseline sleeping characteristics of the insomnia subjects selected. During the 2-week screening period, there was an average of ~10 MOTN awakenings, for both the subjects later assigned to zolpidem (10.2 calls in 14 nights) and those assigned to placebo (10.1 calls).

Review showed that concomitant medication use was fairly evenly balanced in both trials, and was similar to the pattern usually seen with analgesics, multi-vitamins; calcium and estrogen supplements the most commonly reported medications. One subject in Study ZI-12 was listed in the forms as using Oxycodone which could affect sleep characteristics, but the subject was randomized to the placebo group.

There were no significant differences in demographics, and other baseline characteristics between zolpidem and placebo treatment groups for either of the pivotal studies. The groups

were well-balanced demographically, and had very similar characteristics during the screening period.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints are virtually the same for the two pivotal trials, (following MOTN awakening) Latency to Persistent Sleep (LPS) for the PSG trial, and Latency to Sleep Onset (LSO) for the subjective, "at home" trial.

Since the time that the agreements on endpoints were reached with the sponsor, the Agency has been giving more weight in the reviews to NAW and WASO rather than just reliance on TST. The TST was the first of the secondary endpoints for both trials. For the PSG trial, ZI-06-010, the TST showed statistical significance for the 3.5 mg dose (not the 1.75 mg), but failed to do so for Study ZI-12. NAW and WASO were only exploratory endpoints for Study ZI-06-010, but neither showed statistical significance. The NAW and WASO did show statistical significance in the subjective measurements of Study ZI-12 which is interesting, but less reliable.

As an overall review, Study ZI-06-010, for the 3.5 mg dose, showed statistical significance for the primary and all the secondary endpoints, but not for the (exploratory) important measurements of NAW and WASO. Study ZI-12 showed statistical significance for the primary endpoint, but not the first of the secondary endpoints (TST), so the NAW and WASO, although otherwise statistically significant were not counted in support of the application.

Study ZI-06-010 - Primary efficacy endpoint:

- Average latency to persistent sleep after MOTN awakening (LPS_{MOTN}) zolpidem SL 3.5 mg versus placebo.

PSG recordings were scored in 30-second epochs. Latency to Persistent Sleep (LPS) was defined as the number of epochs (30 seconds duration) from the beginning of the recording (following MOTN awakening) to the start of the first 20 minutes asleep divided by 2 to average for the two nights of a treatment. After the MOTN awakening, and being kept awake for 30 minutes, the length of time to fall asleep after the second "lights out" was determined (LPS_{MOTN} is shown in Fig. 11

The primary comparison (primary endpoint) for the trial is only between zolpidem tartrate 3.5 mg and placebo. For review convenience, it is more convenient to discuss at the same time both of the two zolpidem doses in their comparison to placebo. LPS_{MOTN} (after awakening and 30 minute post-dose wait) was 9.7 minutes for the zolpidem SL 3.5 mg group, 16.9 minutes for the zolpidem SL 1.75 mg group, and 28.1 minutes for the placebo group.

Both the zolpidem 3.5 mg and the zolpidem 1.75 mg dosages were statistically significant (at $p<0.001$ each) compared to placebo, and the difference between the 3.5 mg and 1.75 mg doses was statistically significant ($P<0.001$). By comparison to placebo group, sleep latency was

improved (shortened) by 18.4 minutes for the 3.5 mg, and 11.2 minutes by the 1.75 mg doses. The "mean value" above refers to the adjusted or least squares (LS) mean of the variable which was agreed upon in pre-NDA discussions for the statistical analysis. Using the standard mean values (see Table 8) gives a longer LPS (14.2 and 23.7 minutes for the higher and lower zolpidem SL dose respectively, compared to 37.3 minutes for the placebo group (Fig.11). However, the primary endpoint still reaches statistical significance for the trial.

Table 8. PSG Latency to Persistent Sleep after MOTN Awakening (LPS_{MOTN}) – ZI-06-010

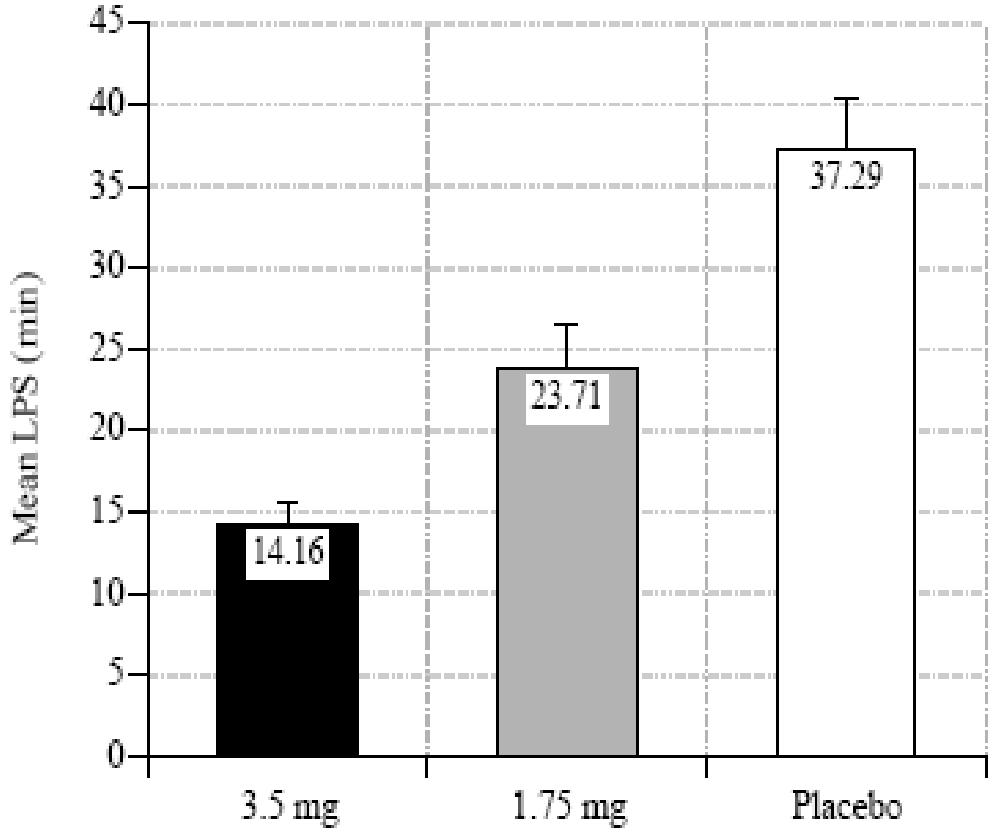
PSG Variable LPS_{MOTN} (min)	**Screening (n=82)**	**3.5 mg (n=80)**	**1.75 mg (n=82)**	**Placebo (n=81)**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
Mean (SEM)	49.8 (2.9)	14.2 (1.4)	23.7 (2.7)	37.3 (3.0)	
Median	45.0	11.3	16.8	29.3	
Min, Max	19.8, 149.0	1.0, 60.5	2.3, 145.5	3.3, 136.0	
ANCOVA Analysis					
LS Mean		9.7	16.9	28.1	
Difference from placebo		18.4	11.2		<0.001, <0.001
95% CI		8.1, 11.7	14.1, 20.3	23.4, 33.8	
Comparison to placebo					
Difference in LS Means		0.34	0.60		
95% CI for Difference		0.28, 0.42	0.49, 0.74		
p-value		<0.001	<0.001		
Comparison of zolpidem SL 3.5 mg to 1.75 mg					
Difference in LS Means		0.57			<0.001
95% CI for Difference		0.47, 0.70			

Source: modified from Study ZI-06-010, Section 11.4.1

The treatment-attributable difference between the groups is a decreased time for return to sleep of 18.4 min., and 11.2 min. for the higher and lower zolpidem doses respectively using LS mean (or 23.1 min., and 13.6 min using SEM). Comparing the active drug phases for the placebo to the baseline/screening phase shows that there was a "placebo effect" of ~ 12.5 minutes decreased sleep latency based on the mean (SEM). This was probably due to increased familiarization with sleeping in the PSG lab, since the placebo drug was administered during the screening phase as well as the active drug phase. Comparison of the second night in the sleep lab to the first night during the screening shows ~ a 10 minute decrease in latency on the second night. Even during

the active drug phases, the second night showed slightly lower (although not significant) sleep latency although by then subjects had already spend three night in the sleep labs.

Fig. 11. Mean (SEM) LPS after MOTN Awakening by Treatment (from PSG)



Source: Clinical Study Report ZI-06-010, appendix

The sponsor did a post-hoc analysis of return to sleep after dosing looking at 10 minute intervals showed that at 10 minutes after lights-out 44%, 23% and 10% of the subjects were asleep for zolpidem 3.5 mg, zolpidem 1.75 mg and placebo, respectively. By 30 minutes after second lights out, 90%, 73% and 51% of the 3.5 mg, 1.75 mg, and placebo groups respectively were asleep.

"Responders" were defined within the trial as subjects with average LPS_{MOTN} <20 minutes, which included 60/80 (76%) of the 3.5 mg group, 46/82 (56%) of the 1.75 mg group and 23/81 (28%) of the placebo group. Analyzing the data excluding subjects with < 5 minute difference from screening LPS made no significant difference.

Study ZI-12 - Primary efficacy endpoint:

- Average Latency to Sleep Onset after MOTN awakening (LSO_{MOTN}) averaged across nights on which subjects took study medication during the 4-week treatment period.

The LSO_{MOTN} was the subject's response to the IVRS diary question, "How long did it take you to fall asleep after taking your study medication?"

The $sLSO_{MOTN}$, for was decreased when averaged across the 4-week treatment period (primary endpoint), and for the individual weeks ($p<0.0001$), as summarized in Table 9. The LS mean LSO_{MOTN} for the zolpidem SL 3.5 mg group was 38.2 minutes averaged over the 4-week trial, compared to 56.4 minutes for the placebo group. The treatment-attributable improvement in LSO_{MOTN} for the zolpidem SL 3.5 mg group is 18.2 minutes. Both the zolpidem and placebo groups felt that their sleep latency was slightly shorter (by 6 to 7 minutes) in the second two weeks compared to the first two weeks.

Table 9. Subjective Latency to Sleep Onset ($sLSO_{MOTN}$) (from TMSQ)(min.) – ZI-12

	zolpidem SL 3.5 mg	**placebo**	**P-value**
Number of Subjects			
Baseline (n)	n = 150	n = 144	
Mean (SE)	73.2 (2.8)	75.2 (3.1)	
Median (min, max)	63.8 (27, 234)	64.0 (27, 255)	
LS Mean	68.1	69.4	0.681
Treatment Weeks 1 to 2 (n)	n = 150	n = 144	
Mean (SE)	49.3 (3.0)	67.6 (2.7)	
Median (min, max)	41.1 (10, 231)	60.6 (12, 177)	
LS Mean	40.1	58.9	<0.0001
Treatment Weeks 3 to 4 (n)	n = 139	n = 134	
Mean (SE)	41.5 (2.4)	62.0 (3.1)	
Median (min, max)	33.3 (4, 180)	54.8 (10, 165)	
LS Mean	33.8	51.7	<0.0001

Source: Clinical Study ZI-12, Section 11.4.1.1

Study ZI-06-010 also assessed Sleep Onset Latency (sLOS) using the TMSQ. This point in the review seems the logical place to discuss the measurement since it was basically the same measurement in both trials, even though it was a secondary endpoint for the sleep-lab trial.

Similar to the subjective under-estimates of TST, subjects over-estimated the lag time between drug administration and sleep (compared to the PSG-recorded information). As shown in Table 10 the TMSQ reported estimates (by LS mean) were more than doubled (2.6 fold) by the zolpidem SL 3.5 group. They estimated a lag of 25.2 minutes compared to the PSG LPS of 9.7 minutes. The gap was not quite as wide while in the 1.75 mg group (28.6 min., a 1.7 fold increase), and placebo group (40.4 min., a 1.4 fold increase), but still very significant over-estimates compared to the PSG for sleep onset. As a secondary endpoint, the comparisons of

both drug doses to placebo reached statistical significance ($p<0.001$), but not the dose-to-dose comparison (0.11).

Table 10. Sleep Onset Latency ($sSOL_{MOTN}$) by Morning Sleep Questionnaire – ZI-06-010

TMSQ Parameter:					
SOL (min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	82	80	82	81	
Mean (SEM)	63.3 (4.4)	33.7 (3.4)	38.0 (3.523)	50.2 (3.871)	
Median	52.5	23.8	30.0	42.5	
Min, Max	12.5, 240.0	7.5, 153.0	5.0, 172.5	10.0, 150.0	
ANCOVA Analysis					
LS Mean		25.2	28.6	40.4	<0.001
Comparison to Placebo					
Difference in LS Means		0.62	0.71		<0.001 <0.001
95% CI for Difference		0.53, 0.73	0.61, 0.82		
Comparison of zolpidem tartrate lozenge 3.5 mg to 1.75 mg					
Difference in LS Means		0.88			0.111
95% CI for Difference		0.76, 1.03			

The primary value of the measurement is probably that it allows comparison of a subjective measurement of efficacy between the two trials. The response to the morning questionnaire shows marked similarity in the pattern of responses in both trials, and is consistent with the PSG data.

6.1.5 Analysis of Secondary Endpoints

Many of the secondary endpoints rely on subjective responses to the Treatment Morning Sleep Questionnaire (TMSQ) which includes the following self-ratings:

1. LOS post-dose (minutes): length of time it took to fall asleep after the second lights-out
2. Subjective TST post-dose (minutes): duration of sleep in minutes after the second lights-out
3. Subjective NAW post-dose: sNAW after the second lights-out

4. Duration of awakenings post-dose (minutes): sum of the amount of time the patient reported it took to fall asleep again following each awakening after the second lights-out
5. Rating of sleep quality: patient self rating score, where 1 = poor, 2 = fair; 3 = good; and 4 = excellent
6. Rating of level of refreshed sleep: patient self-rating score, where 1 = poor, 2 = fair; 3 = good; and 4 = excellent
7. Rating of ability to function: patient self-rating score, where 1 = poor, 2 = fair; 3 = good; and 4 = excellent

There is overlap of the secondary and exploratory endpoints for the two trials (i.e., an assessment that is a secondary endpoint for one may be an exploratory endpoint for the other trial).

In this review, the various strata of endpoints may reviewed together to allow for ease of comparison of the findings. Some of the secondary and exploratory endpoints have already been reviewed with the primary endpoint, such as sLSO by TMSQ, to allow comparison to the primary sleep latency findings. The secondary endpoints are (in order of hierarchy):

Study ZI-06-010
1. Total Sleep Time (TST by PSG)
2. Sleep Efficiency (by PSG)
3. Sleep Quality (by TMSQ)
4. Latency of Sleep Onset (sLSO by TMSQ)

Study ZI-12
1. Subjective Total Sleep Time (sTST)
2. Number of Awakenings (sNAW)
3. Waketime After Sleep Onset (sWASO)

Total Sleep Time (TST) - ZI-06-010:

Both of the pivotal trials used zolpidem SL 3.5 mg versus placebo Total Sleep Time (TST_{MOTN}) as the first of the secondary endpoints. TST is defined as the sum of the Total Sleep Time in minutes, after the second lights out (in ZI-06-010), or after taking the study medication (ZI-12).

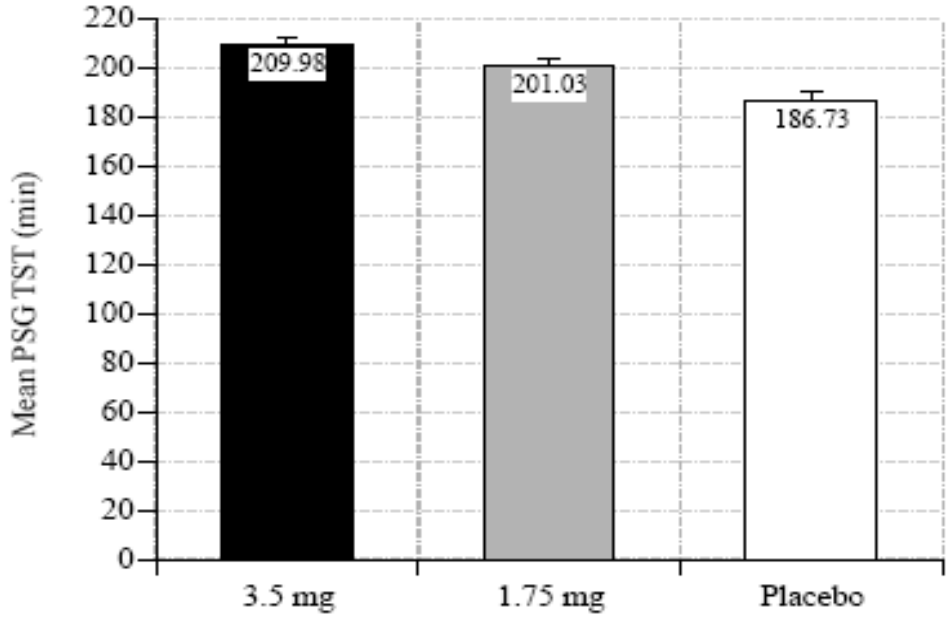
As shown in Table 11 there was an increased sleep time (by PSG) for the placebo group of ~ 12 minutes over baseline/screening for the 4 hours following MOTN and drug administration. Again, this may have been due to increased familiarization with sleeping in the PSG lab. There was a nearly 18 minute increase in sleeping time on the second night in the sleep lab compared to the first night during the screening phase, and slight increases in all groups on subsequent nights. The increased sleep time attributable to zolpidem (using LS mean) was ~26 min. for the 3.5 mg, and 15 min. for the 1.75 mg dose which reached statistical significance compared to placebo ($p<0.001$ for each). The change using standard mean was similar using LS means, showing ~23 min. of increased post MOTN sleep time for 3.5 mg, and 14 min. for 1.75 mg zolpidem SL. The resulting sleep time indicates that of the 240 min. (4 hours) of bed time remaining after MOTN, the 3.5 mg group slept ~$3^1/_2$ hours, the 1.75 mg group slept ~ $3^1/_4$ hours, and the placebo group slept ~3 hours. The 11.2 min. difference between the two zolpidem doses showed statistical significance for their comparison ($p=0.005$).

Table 11. PSG Total Sleep Time (min.) after MOTN Awakening (TST_{MOTN}) – ZI-06-010

TST_{MOTN}(min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	82	80	82	81	
Mean (SEM)	174 (4)	210 (2)	201 (3)	187 (4)	
Median	183	214	209	195	
Min, Max	23, 219	109, 234	59, 230	60, 234	
ANCOVA Analysis					
LS Mean		209.0	197.8	183.1	
Difference from placebo		25.9	14.7		<0.001 each
Comparison of doses		11.2			0.005

Source:
Comparison of study sites and sequence showed only minor differences, more noticeable between sites than between sequences, but not statistically significant for any site. Differences were due mainly to outliers that are reflected in the min/max ranges listed in the charts.

Fig. 12. Mean PSG Total Sleep Time (TST) after MOTN Awakening by Treatment – ZI-06-010



Source: Clinical Study Report ZI-06-010, appendix

Average subjective TST (sTST) was also collected data in this trial from TMSQ.
The sTST ratings in ZI-06-010 estimated post-awakening sleep time as 173 min., 162 min., and 149 min., for zolpidem SL 3.5 mg, 17.5 mg and placebo, respectively. The data derived from the

TMSQ reached statistical significance for both zolpidem SL 3.5 mg and 1.75 mg (<0.001, and 0.01 respectively) compared to placebo, but not by dose-to-dose comparison (p=0.06).

The usefulness of the information is primarily in the comparison of the PSG data to the subjects' perceptions. Subjects consistently gave lower estimates of their post MOTN sleep time. The subjects under-estimated the sleep time by 17%, 18%, and 19% for zolpidem SL 3.5 mg, 17.5 mg and placebo, respectively. The sponsors of sleep aid medications are often reluctant to use PSG trials. The difference between the subjective and objective data obtained in trials such as this should be an added incentive to include the sleep lab trials to improve the efficacy profile of the study drug, and adds to the Agency's assertion that the PSG trials provide a more accurate assessment of the clinical effects of a drug.

Total Sleep Time (TST) - ZI-12

All secondary efficacy endpoints were evaluated for the nights on which the subjects took the study medication during the treatment period. They are listed by order of hierarchy in which they were analyzed. Each of these refers to evaluations on time following middle-of-the-night awakening.

As previously discussed, the analysis of the first of the secondary endpoints (sTST) for this trial did not show significance, so the secondary endpoints were considered as exploratory rather than supportive of the application. However, the endpoints were reviewed for any evidence of inconsistency with other data from either pivotal trial, and for any information that could be provided on use of the drug over a more extended time frame than the PSG trial provided.

The $sTST_{MOTN}$ (for both the screening and active treatment phases) was based on the response to the IVRS question: "After you fell back to sleep, how long did you sleep until you woke up this morning?" The response was recorded in number of minutes, and only for the nights in which the assigned study drug was taken.

The $sTST_{MOTN}$ endpoint analysis did not reach statistical significance (p=0.34), but showed improved TST favoring the zolpidem group.

Analysis of the Total Sleep Time endpoint ($sTST_{MOTN}$) was complicated by a difference in the baseline/screening phase difference in TST between the two groups. During the 2 week screening, the subjects later randomized to zolpidem reported sleeping time (after MOTN and taking the placebo) as18 minutes longer than the average time reported by subjects later randomized to the placebo group (Table 12).

The zolpidem group reported LS mean sTST of ~241 min. during the 2-week baseline, and a sTST of 264 min. during the active study phase, giving an improvement in TST of 23 minutes. The placebo group reported a TST of 223 min. during screening and a TST of 255 during the active study period, for an improvement of 32 minutes. The sponsor explains this difference by the baseline/screening phase difference in sTST between the two groups. The TST reports are subjective, so over-estimation or under-estimation of sleep time occurs. The 18 minute

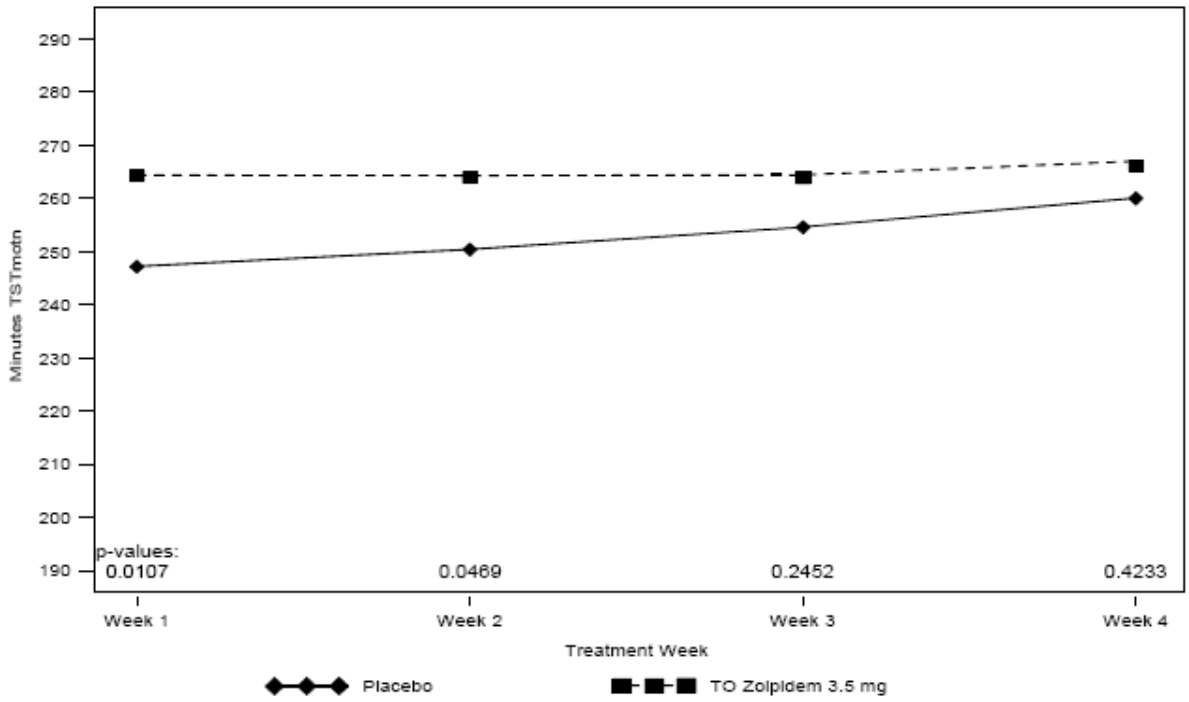
difference between the groups at baseline is large enough to be significant, but with the size of the groups, the difference may represent a basic difference in insomnia. Looking to see what percentage improvement each group reported consisted of comparing the change in each group to their own baseline TST rather than comparison of zolpidem to placebo groups. This shows a TST improvement of 9.5% for the zolpidem group, and 14.4% improvement for the placebo group. Looking at the data by individual weeks shows that the zolpidem increased the reported TST in the first week, and TST remained stable (not varying more than 2 minutes per week) during the subsequent 3 weeks. The reported TST of the placebo group increased in the first week and increased a few minutes in each subsequent week (TST of 247 min at the end of Week 1 to 255 by the end of Week 4). (see Fig. 13)

Table 12. Subjective TST_{MOTN} (min) (Efficacy Population) – ZI-12

	zolpidem SL 3.5 mg	**placebo**	**p-value**
Number of Subjects	150	144	
Baseline			
Mean (SE)	242.0 (5.75)	224.0 (6.57)	
Median (min, max)	240.0 (33, 477)	222.5 (12, 433)	
LS Mean (SE)	241.2 (6.19)	222.9 (6.30)	0.0341
Treatment Change			
Mean (SE)	270.7 (5.6)	246.9 (7.2)	
Median (min, max)	270.0 (70, 450)	247.8 (55, 420)	
LS Mean (SE)	264.1 (4.2)	255.0 (4.3)	0.128
Change from baseline	22.9	32.1	
Change from placebo	N.A..*		

* N. A. due to baseline imbalance Source: Clinical Study ZI-12, Section 11.4.1.1

Fig. 13. ANCOVA Estimates of $sTST_{MOTN}$ (min) on Dosing Nights



Source: Clinical Study ZI-12, Section 11.4.1.1

Sleep Efficiency (SE):
SE was an endpoint only in the ZI-06-010 trial, and only for the zolpidem 3.5 mg dose versus placebo.

Sleep Efficiency (SE) is defined as (Total Sleep Time after middle-of-the-night awakening divided by total time in bed) x 100 for a percentage. Based on LS means, the SE is 87%, 83%, and 76% for zolidem SL 3.5 mg, 1.75 mg and placebo, respectively. The "placebo effect" (comparison of the placebo group to baseline) is 5.3%, and treatment-attributable effect is 5.5% for the zolpidem SL 3.5 mg, and 1.0% for the zolpidem SL 1.75 dose. Having already provided evidence of efficacy in the TST endpoint, a sleep efficacy endpoint is rather redundant, and fails to provide much useful information on the drug, especially since NAW and WASO were not significantly improved in this trial.

Sleep Quality
Sleep quality was assessed on a 9-point ordinal scale that was scored as 1=extremely poor to 9=excellent. Sleep Quality is #3 of the secondary endpoints for Study ZI-06-010, and an exploratory endpoint for Study ZI-12. The self-assessment ratings for Sleep Quality (along with Ability to Function, and Level of Refreshed Sleep are obtained from the TMSQ.

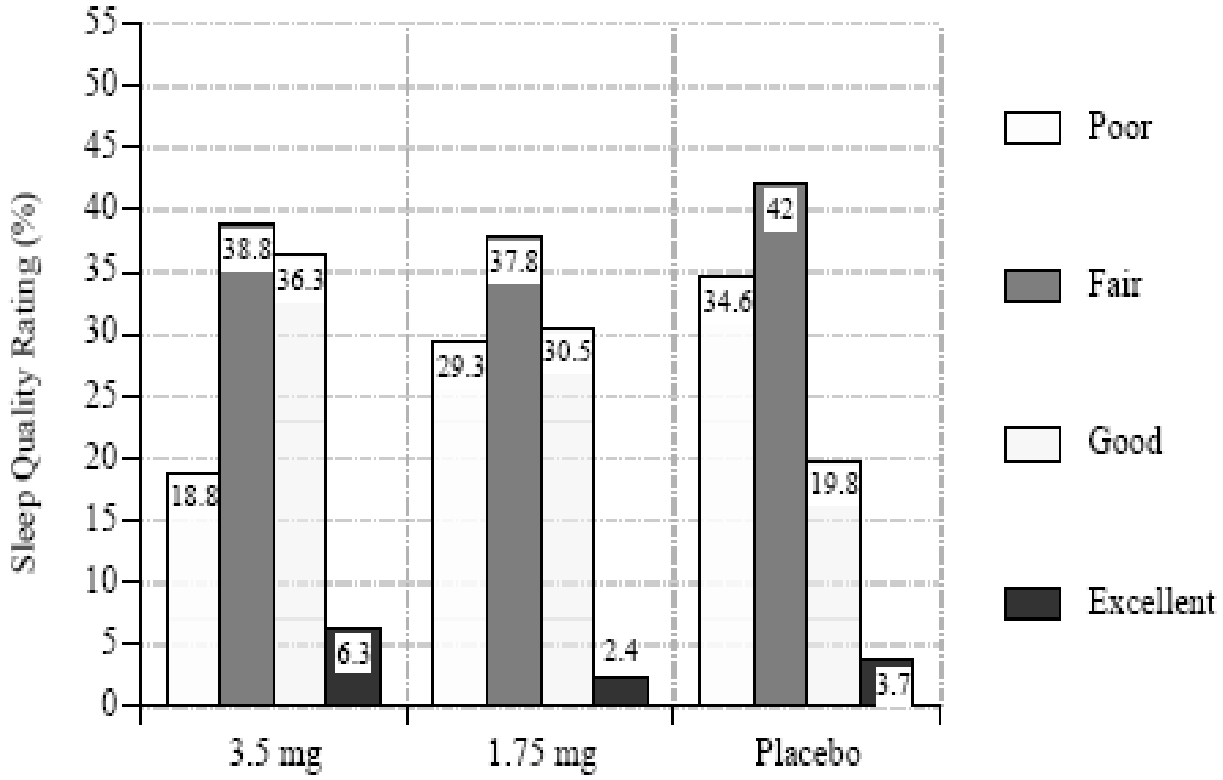
In Study ZI-06-010, the Sleep Quality was rated on the TMSQ as "good" by ~16% of the subjects during screening, and as "good or excellent" by 24% while on placebo phase of the

active drug study. By comparison, a rating of "good or excellent" was reported by ~42% of the zolpidem SL 3.5 mg group, 33% of the 1.75 mg, groups, and 24% of the placebo group.(Table 13 and Fig. 14). The assessment reached statistical significance for zolpidem SL 3.5 mg ($p<0.001$), but not for the 1.75 mg dose ($p=0.18$). Although the SQ ratings improved for the zolpidem groups, a rating of "excellent" was quite scarce, and in that category the placebo group outscored the zolpidem 1.75 mg group.

Table 13. Sleep Quality, Level of Refreshed Sleep, and Ability to Function (from TMSQ) – - Study ZI-06-010

TMSQ Parameter:					
	Screening	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Sleep Quality					
N	82	80	82	81	Overall: < 0.001
Poor	38 (46.3%)	15 (18.8%)	24 (29.3%)	28 (34.6%)	3.5 mg vs. Placebo: < 0.001
Fair	31 (37.8%)	31 (38.8%)	31 (37.8%)	34 (42.0%)	1.75 mg vs. Placebo: 0.116
Good	13 (15.9%)	29 (36.3%)	25 (30.5%)	16 (19.8%)	3.5 mg vs. 1.75 mg: 0.018
Excellent	0 (0.0%)	5 (6.3%)	2 (2.4%)	3 (3.7%)	
Level of Refreshed Sleep					
Poor	36 (43.9%)	14 (17.5%)	18 (22.0%)	26 (32.1%)	3.5 mg vs. Placebo: < 0.001
Fair	34 (41.5%)	34 (42.5%)	34 (41.5%)	36 (44.4%)	1.75 mg vs. Placebo: 0.017
Good	12 (14.6%)	28 (35.0%)	28 (34.1%)	16 (19.8%)	3.5 mg vs. 1.75 mg: 0.332
Excellent	0 (0.0%)	4 (5.0%)	2 (2.4%)	3 (3.7%)	
Ability to Function					
Poor	21 (25.6%)	6 (7.5%)	8 (9.8%)	15 (18.5%)	3.5 mg vs. Placebo: 0.009
Fair	35 (42.7%)	33 (41.3%)	35 (42.7%)	34 (42.0%)	1.75 mg vs. Placebo: 0.024
Good	24 (29.3%)	36 (45.0%)	34 (41.5%)	27 (33.3%)	3.5 mg vs. 1.75 mg: 0.355
Excellent	2 (2.4%)	5 (6.3%)	5 (6.1%)	5 (6.2%)	

Fig. 14. Sleep Quality Rating (%) from the TMSQ after MOTN Awakening by Treatment – ZI-06-010



Source:

Sleep Quality - ZI-12
A sleep quality rating was recorded every morning regardless of whether a subject took a dose of study medication. Significant improvement in SQ was reported by the zolpidem group compared to the placebo group for the over the whole trial, and by each week. There was no significant difference in sleep quality between zolpidem and placebo groups in SQ ratings on the nights that study drug was not used.

NAW and WASO
NAW and WASO were secondary endpoints for Study ZI-12, and exploratory endpoints for Study ZI-06-010. These measures were below the cut-off on the hierarchy for the former trial, and did not show significance for the drug doses compared to placebo in the latter trial. They are included in this review because of their importance in the general review of all sedative-hypnotic drugs. The Agency agreed that the sponsor would not be required to prove efficacy on any measure other than return to sleep after middle-of-the-night awakening. It would be difficult to consider a drug effective for insomnia if either NAW or WASO increased with the drug use.

In Study ZI-06-010, the NAW (PSG-monitored) was decreased compared to placebo after both zolpidem 3.5 mg and 1.75 mg, but the difference was very slight, and not statistically significant

(P=0.072). The number of subsequent awakening decreased only from 4.1 (placebo) to 3.7 awakenings (both zolpidem doses). (see Table 14). This raised concern in the review process about safety since with subsequent awakenings, patients may be at increased risk if they are sedated.

Table 14. PSG Number of Awakenings after MOTN Awakening (NAW_{MOTN}) – ZI-06-010

PSG Parameter: NAW_{MOTN}	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	82	80	82	81	
Mean (SEM)	4.0 (0.2)	3.7 (0.20)	3.7 (0.3)	4.1 (0.3)	
Median	3.5	3.5	3.0	4.0	
Min, Max	0.0, 11.5	0.5, 10.0	0.0, 15.0	0.5, 10.5	
ANCOVA Analysis					
LS Mean		3.7	3.7	4.1	
Comparison to Placebo		0.4	0.4		0.049 (3.5 mg) 0.045 (1.75 mg)

In Study ZI-06-010, subjects were asked each morning how many awakenings they had the previous night. The responses show that the subjects consistently under-estimate the number of awakening compared to the PSG recordings (Table 15), and are aware of, or recall, only ~about one-third of their MOTN awakenings.

Table 15. Subjective Number of Awakenings after MOTN Awakening ($sNAW_{MOTN}$)

TMSQ Parameter: $sNAW_{MOTN}$ (min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	82	80	82	81	
Mean (S.E.)	1.7 (0.1)	1.2 (0.1)	1.3 (0.9)	1.4 (0.1)	
Median	1.5	1.0	1.0	1.5	
Min, Max	0.0, 5.5	0.0, 5.0	0.0, 4.0	0.0, 4.5	
ANCOVA Analysis					
LS Mean		0.86	1.03	1.14	0.017
Comparison to Placebo					
Difference in LS Means		0.75	0.90		
P-value		0.005	0.301		

The Subjective Number of Awakenings ($sNAW_{MOTN}$) in Study ZI-12 (after taking the study medication) were based on the recorded response to IVRS question, "After you fell back to sleep, how many times did you wake up again before waking up in the morning?"

During the 2-week screening/baseline, there were differences between the groups at baseline (in the 0 awakenings and >2/night categories), but did not reach statistical significance. (Table 16).

Post treatment, the percentage reporting “no additional awakenings” in the zolpidem group increased by 13.3% compared to their baseline or to the placebo group (which reported a 4.9% increase). Correspondingly, the percentage of the zolpidem group reporting >2 additional awakenings decreased (by 4.7 %) compared to their baseline, while the placebo group remained stable. There is a treatment-attributable improvement in the zolpidem group of 13% in the “no awakenings”, and decrease of 8.6% in the “> 2 awakenings” categories compared to the placebo group. The majority of the subjects in the middle groups (between 0 and 2 subsequent awakenings remained unchanged form baseline. The results are consistent with the subjective responses to the question in Study ZI-06-010 which suggests that subjects may be experiencing more awakenings post-treatment, but they may not reach the level of awareness, or they are poorly recalled.

Table 16. Subjective Number of Awakenings $sNAW_{MOTN}$ (%) – ZI-12

	zolpidem SL 3.5 mg	**placebo**	**p-value**
Average $sNAW_{MOTN}$ Reported	**% patients reporting**		
Baseline Average			0.160
0 awakenings	16.7%	11.8%	
>0 and ≤1 awakening	46.0%	45.1%	
>1 and ≤2 awakenings	26.0%	27.1%	
>2 awakenings	11.3%	16.0%	
Treatment Average			*
No Awakenings	44.5% (30.0%)	32.8% (16.7%)	
>0 and ≤1 awakening	30.6% (46.0%)	33.0% (43.1%)	
>1 and ≤2 awakenings	18.4% (17.3%)	19.3% (25.0%)	
> 2 Awakenings	6.6% (6.7%)	15.0% (15.3%)	

*statistical findings not applied to NDA evaluation due to endpoint hierarchy
Source: modified from Clinical Study ZI-12, Section 11.4.1.1

Average Wake Time After Sleep Onset (WASO)

The PSG-monitored WASO data from Study ZI-06-010 (Table 17) shows that mean $sWASO_{MOTN}$ was ~ 15 minutes for all three treatment periods, and no significant change from baseline.

Table 17. PSG Wake Time After Sleep Onset after MOTN Awakening – ZI-06-010

PSG Parameter: WASO (min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**
Mean Days 1 and 2, Post MOTN Awakening				
N	82	80	82	81
Mean (SEM)	22.6 (1.9)	20.7 (2.0)	22.9 (2.8)	22.2 (2.1)
Median	17.4	15.0	15.0	15.0
Min, Max	1.0, 73.8	2.3, 104.0	2.0, 160.3	1.8, 86.5
ANCOVA Analysis				
LS Mean		15.1	15.8	15.7
Comparison to Placebo				
Difference in LS Means		1.0	1.0	
P-value		0.584	0.932	

Comparison of zolpidem tartrate lozenge 3.5 mg to 1.75 mgb p=0.527

In Study ZI-06-010, $sWASO_{MOTN}$ was derived from the TMSQ. Subjects were instructed that it meant time awake during the additional post-dose awakenings, but excluding the time awake immediately after MOTN awakening when the study medication was taken. The post-hoc analyses of $sWASO_{MOTN}$ showed a decrease in sWASO between baseline and post-treatment for all 3 periods, but differences between the zolpidem groups and the placebo period showed only slight changes of ~ 5.5 minutes decrease for the 3.5 mg , and 4.8 minutes for the 1.75 mg periods compared to placebo.

Table 18. Subjective Wake Time After Sleep Onset ($sWASO_{MOTN}$) – ZI-06-010

TMSQ Parameter: $sWASO_{MOTN}$ (min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	75	67	74	70	
Mean (S.E.)	54.7 (5.1)	35.8 (2.7)	39.0 (3.4)	41.8 (3.2)	
Median	45.0	30.0	30.0	33.8	
Min, Max	5.0, 287.5	5.0, 105.0	4.0, 160.0	7.5, 130.0	
ANCOVA Analysis					
LS Mean		28.7	29.4	34.2	0.08
Comparison to Placebo					
Difference in LS Means		0.84	0.86		
P-value		0.04	0.07		
Comparison of zolpidem 3.5 mg to 1.75 mg					
Difference in LS Means		0.97			0.761

In Study ZI-12, the $sWASO_{MOTN}$ was based on the response to the IVRS question: "Considering all of these awakenings (after taking study medication and returning to sleep), how long were you awake from the time you went back to sleep after dosing until you got out of bed this morning?"

There were differences between the two groups at baseline with the group later assigned to zolpidem more frequently reporting no additional awake time (16.7% compared to 11.8% for placebo), but the groups were nearly equal in the percentage reporting additional awake time of >60 minutes (39.2% and 41.0% for the zolpidem and placebo groups respectively). The differences did not reach statistical significance.

The active treatment phase data for the $sWASO_{MOTN}$ shows a increase for the zolpidem group of subjects reporting no additional time awake (an increase of 27.8% over baseline compared to 21.0% for placebo), giving a treatment-attributable effect of 7.8% favoring zolpidem. Looking at the subjects reporting > 60 minutes additional awake time during the additional awakenings, the zolpidem group decreased the percentage 20.0% (compared to baseline), and the placebo group decreased by 15.1%, giving a treatment-attributable decrease of 4.9% favoring zolpidem.

Table 19. Subjective Wake Time (min) After Sleep Onset Post Middle-of-the-Night Awakening ($sWASO_{MOTN}$) (by %)

Average Wake Time After Sleep Onset	**zolpidem SL 3.5 mg**	**placebo**	**Overall P-value**
	% Patients Reporting		
Baseline			0.512
No Wake Time	16.7%	11.8%	
>0-20 Minutes	18.7%	14.6%	
21-60 Minutes	25.3%	32.6%	
> 60 Minutes	39.3%	41.0%	
Treatment Average			
No Wake Time	44.5% (30.0%)	32.8% (16.7%)	
>0-20 Minutes	18.5% (27.3%)	17.1% (26.4%)	
21-60 Minutes	17.5% (26.0%)	24.3% (31.9%)	
> 60 Minutes	19.6% (16.7%)	25.9% (25.0%)	

*statistical findings not applied to NDA evaluation due to endpoint hierarchy
Source: modified from Clinical Study ZI-12, Section 11.4.1.1

6.1.6 Other Endpoints

Most of the exploratory efficacy endpoints have been discussed in the section above.

Study ZI-12 included an exploratory efficacy endpoint on Total Score from the Insomnia Severity Index (ISI). The ISI is a general insomnia questionnaire, not specifically designed to assess middle-of-the-night awakening. It was administered at baseline (the end of the 2-week single-blind screening period (Visit 2), at Treatment Day 14 (Visit 3), and Treatment Day 28 (Visit 4), or at the end of treatment if the subject discontinued the study. The index includes following questions to evaluate the prior 2 weeks and was scored as shown:

Question 1 Please rate the current (i.e., last 2 weeks) severity of your insomnia problem(s).

1a Difficulty falling asleep (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe)

1b Difficulty staying asleep (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe)

1c Problem waking up too early (0=none; 1=mild; 2=moderate; 3=severe; 4=very severe)

Question 2 How satisfied/dissatisfied are you with your current sleep pattern? (0=very satisfied to 4=very dissatisfied)

Question 3 To what extent did you consider your sleep problem to interfere with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc)? (0=not at all interfering; 1=a little, 2=somewhat, 3=much; 4=very much interfering)

Question 4 How noticeable to others do you think your sleeping problem is in terms of impairing the quality of your life? (0=not at all noticeable; 1=a little, 2=somewhat, 3=much; 4=very much noticeable)

Question 5 How worried/distressed are you about your current sleep problem? (0=not at all; 1=a little, 2=somewhat, 3=much; 4=very much)

The ISI results, were balenced between treatment groups at baseline (mean score of 18.1 for zolpidem group, and 18.3 for placebo group. At Week 2 and Week 4, the mean scores ranged between 15 and 17 for both treatments. There were no statistically significant differences between the two groups.

Post-hoc analyses of LSO_{MOTN} by gender and race were unremarkable, so the analysis was not extended to the other endpoints.

6.1.7 Subpopulations

In the mITT population of Study ZI-06-010, all subjects by definition had at least 3 baseline MOTN awakenings ≥ 30 minutes per week. Of these, 38/82 (46.3%) subjects had an average post-MOTN awakening total awake time ≥ 60 minutes (from PSG) at baseline (screening); these subjects were evaluated as a subset considered to have more pronounced insomnia. The data for this sub-group was included in this review with the discussion of various endpoints. As shown in Table 20, there was a significant change from baseline for all 3 periods. The LPS_{MOTN} adjusted means were 23.3 minutes, 12.6 minutes, and 37.9 min. for the zolpidem 3.5 mg ($p<0.001$), 1.75 mg ($p=0.003$), and placebo, respectively.

Table 20. LPS_{MOTN}: for Subjects with Screening LPS_{MONT} ≥60 minutes (from PSG)

PSG LPS_{MOTN} (min)	**Screening n=38**	**3.5 mg n=37**	**1.75 mg n=38**	**Placebo n=37**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
Mean (SEM)	65.9 (4.7)	17.0 (2.4)	30.7 (5.0)	44.6 (5.2)	
Median	60.8	12.0	22.3	38.3	
Min, Max	20.3, 149.0	1.0, 60.5	2.3, 145.5	3.3, 136.0	
ANCOVA Analysis					
LS Mean		12.6	23.3	37.9	<0.001
Comparison to Placebo					
Difference in LS Means		0.33	0.61		
p-value		<0.001	0.003		
Comparison of zolpidem tartrate 3.5 mg to 1.75 mg					
Difference in LS Means		0.54			<0.001

PSG Total Sleep Time after MOTN awakening (TST_{MOTN}) was also evaluated for the subjects with baseline LPS_{MOTN} time ≥60 minutes. All periods showed marked improvement form baseline (Table 21). Zolpidem SL showed dose-related increases which were statistically significant compared to placebo for both doses, but did not reach significance for dose-to-dose comparison.

Table 21. $TST_{MONT:}$ for Subjects with Screening LPS_{MONT} ≥60 minutes (from PSG)

TST_{MOTN}(min)	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**	**P-value**
Mean Days 1 and 2, Post MOTN Awakening					
N	38	37	38	37	
Mean (SEM)	150 (5)	204 (4)	192 (6)	177 (6)	
Median	160	208	199	182	
Min, Max	23, 181	109, 234	59, 229	60, 232	
ANCOVA Analysis					
LS Mean		194.6	180.0	166.6	
Difference from placebo		28.0	13.4		<0.001 (3.5 mg) 0.027 (1.75 mg)
Comparison of		14.6			0.024

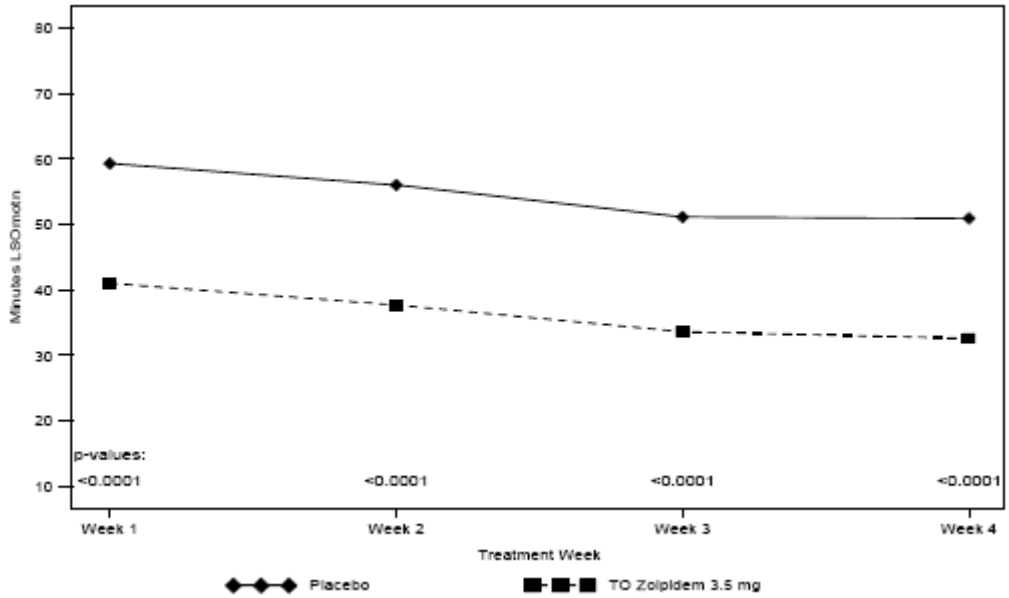
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Zolpidem tartrate SL 1.75 mg also produced statistically significant improvements in efficacy responses compared to placebo, but to a lesser extent than the 3.5 mg dose strength. Comparison of responses among treatments for the various efficacy variables consistently indicated a statistically significant dose-response relationship. The 1.75 mg dose strength was administered only in Study ZI-06-010 in the Phase 3 trials. Review of the Phase I and Phase 2 PK/PD trials showed consistency in the dose relationship and clinical responses. As previously discussed, the 1.75 mg dose strength was formulated for use in the elderly, but only single-dose PK data was available for review for that age group.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Comparison of the individual weeks was done to determine if any change in efficacy occurred over time. Comparing Week 1 to Week 4 data shows a decrease in LSO_{MOTN} for both the zolpidem and placebo groups. The LSO_{MOTN} for zolpidem group was 42 min. for Week 1, and 33 min. for Week 4. There may have been a "placebo effect" to take into account since corresponding Week 1 and Week 4 values for the placebo group were 59 min. and 51 min. respectively. The 8.4 minute difference is similar to the 9 minute difference for the zolpidem group, so there was no evidence of loss of effectiveness. The trial was evaluated to determine whether frequency of study drug use change over the 4-week period, to try to evaluate both duration of effectiveness and possible development of tolerance. A distribution plot of the time of the middle-of-the-night calls is represented in Fig. 15.

Fig. 15. ANCOVA Estimates of LSO_{MOTN} (min) on Dosing Nights



Source: Appendix, Study ZI-12

Frequency of use of the zolpidem closely parallels the use of the placebo. Both decline slightly over the course of the study suggesting that drug dependency does not increase over time, and since the decline is relatively small it might suggest that efficacy is maintained, however persistence of use of the placebo drug at a similar rate prohibits any definite conclusion.

6.1.10 Additional Efficacy Issues/Analyses

7 Review of Safety

Safety Summary

The safety review included safety data from all trials that administered the 3.5 mg or 1.75 mg dose strengths of zolpidem tartrate SL. There were no deaths reported during this clinical development program. The only serious AEs did not involve subjects on active drug treatment, and withdrawals/discontinuations were generally not drug-related.

In the pooled safety data, the most frequently reported AEs were somnolence and fatigue, as expected in with a sedative-hypnotic drug, especially in the daytime trials. Headache was reported by 5.5% of subjects receiving zolpidem 3.5 mg, and by 3.1% of subjects in the 1.0/1.75 mg dose strength groups.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The zolpidem tartrate SL development program consists of 8 trials (Studies ZI-05-009, ZI-13, ZI-14, ZI-15, ZI-16, ZI-17, and the pivotal trials ZI-06-010, and ZI-12). This NDA review includes safety data from all the trials. All the trials in the development program have been completed, and the database results submitted for review. All patients randomized and exposed to at least one dose of the study treatment are included in the safety review. A total of 436 subjects received 3.5 mg zolpidem tartrate sublingual lozenge, 130 subjects received 1.0 mg/1.75 mg, and 315 subjects received placebo.

The trials varied in design, dosages, type of subjects, and duration. The Phase 1 trials with healthy volunteers were included in the pooled safety data along with the subjects with insomnia, and placebo and non-placebo trials, as were open-label and double-blind trials. Trial designs used included parallel-group, cross-over groups, daytime and nighttime trials. All were fixed-dose trials that administered the zolpidem SL 3.5 mg in each, but the 1.75 mg dose was used in only some of the trials, and the 1.0 mg dose only in a few of the early Phase 1 dose-ranging trials.

The Statistical Analysis Plan for the ISS was submitted to the Agency for review (December 10, 2007, doc. 0059). In the minutes of the pre-NDA meeting, (Pre-NDA Meeting Minutes of May 01, 2008), the Agency agreed that the presentation in the submitted SAP would be sufficient for the clinical review team.

For the review summary, focus is on the pooled safety data for the 8 IND trials, and a review of the safety data from the pivotal trials individually. The pooled IND trials (Phase 1 and Phase 3 by the sponsor's trial labeling, no trials were designated Phase 2) include the pivotal trials. Safety in the clinical trials was assessed by review of adverse events, vital signs, laboratory parameters, electrocardiogram (ECG), and residual sedation measurements. Most of the trials used a cross-over design, so the subjects receiving the active study drugs were compared to themselves while receiving placebo. The exception is the pivotal trial ZI-12 which used a parallel-group design.

The subject data base was checked during review to see if subjects were randomized more than once (for all subjects in the pivotal trials, and spot-checked (~10%) for all additional trials. Subjects were checked by sites, birth dates, initials, gender, and race. There was no evidence of duplication in the database files.

For the long-term safety of the drug, the sponsor relies on the reference listed drug, Ambien®. The reliance was accepted by the Agency (EOP2 Meeting Minutes, February 06, 2007). The longest use of the study drug in the clinical trials was the 4-week pivotal "at-home" trial where the medication was used on an as-needed basis. The Agency agreed (Pre-NDA Meeting Minutes of May 01, 2008) that the data from Study ZI-12 could serve as the primary data source for the treatment-emergent adverse event (TEAE) table (Section 6.1) of the package insert.

7.1.2 Categorization of Adverse Events

Adverse event categorization and preferred terms used in coding were referenced to the MeDRA dictionary (version 10.0) and provided in the transport file. During the review, I audited the CRFs, the narratives of SAEs and withdrawals associated with AEs, and special interest events such as the data collected on residual effects. No systematic errors in coding were found.

Subjects are only counted once for each level of summarization (system organ class, preferred term). The tables of AEs represent reported event terms with a frequency of > 1% occurrence. In assigning AEs to treatment periods, if an AE worsened when starting a new treatment period, subjects were counted again under the new period.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The ISS provided by the sponsor provided a database for review of AEs in the pooled group of all 8 IND studies in the product development, and the data was compared to the AEs reported for each of the IND trials. Common adverse events are discussed in Section 7.4.1, non-fatal serious adverse events in Section 7.3.2, and significant adverse events in Section 7.3.4.

7.2 Adequacy of Safety Assessments

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

Eight IND Studies are included in the safety data review: (Studies ZI-05-009, ZI-13, ZI-14, ZI-15, ZI-16, ZI-17, and the two pivotal trials ZI-06-010, and ZI-12). All the trials were conducted in the United States. Table 22 shows the demographic characteristics of the pooled dose groups.

Dose groups were balanced with respect to demographic characteristics, except that elderly subjects were included in only one early phase study, and excluded in the pivotal trials. Overall, 65% of subjects were Caucasian, and 62% were female. Mean subject age was 41 years (range: 18 to 83 years), with 95.9% of subjects under the age of 65 years. Characteristics such as height and weight have not been included in the table since differences between the groups were very slight.

Table 23 presents the information on subjects in the pooled INDs that were exposed to one dose or more of zolpidem tartrate SL. Most of the exposures occurred in cross-over trials, but all exposures are included. The Total column shows the total number of subjects who received one or more doses of study medication, independent of treatment received.

Table 22. Demographic Characteristics Pooled (8) IND Studies (Safety Population)

Variable	**1.0-mg/1.75-mg zolpidem SL**	**3.5-mg zolpidem SL**	**placebo**	**Total**
Number of Subjects	**130**	**436**	**315**	**585**
Age				
Mean (SD)	48.2 (15.8)	40.6 (14.1)	40.7 (12.1)	41.2 (13.6)
Median	46.0	40.0	41.0	41.0
Range	19 - 83	18 - 83	18 - 64	18 - 83
Age category				
<65 Years	106 (81.5%)	413 (94.7%)	315 (100%)	561 (95.9%)
≥65 Years	24 (18.5%)	23 (5.3%)	0	24 (4.1%)
Sex [n (%)]				
Male	45 (34.6%)	172 (39.4%)	124 (39.4%)	223 (38.1%)
Female	85 (65.4%)	264 (60.6%)	191 (60.6%)	362 (61.9%)
Race [n (%)]				
Caucasian	75 (57.7%)	282 (64.7%)	190 (60.3%)	378 (64.6%)
Non-Caucasian	55 (42.3%)	154 (35.3%)	125 (39.7%)	207 (35.4%)

Subjects in crossover studies ZI-05-009, ZI-06-010, ZI-13, ZI-14, ZI-15, ZI-16, and ZI-17 received more than one treatment and are included in more than one column, based on the treatments actually received.

Since zolpidem SL is at maximum to be taken only once in a 24-hour period, the number of study drugs received is also the total of exposure days. The 1.0 mg dose of zolpidem SL was administered only in the early Phase 1 trials, and discontinued due to lack of effectiveness. The 1.75 mg dose was administered in some of the early phase trials, and in only the shorter of the two pivotal trials (ZI-06-010). The longest exposure to the study drug was in the pivotal "at home" 4-week trial (ZI-12) which used only zolpidem SL 3.5 mg and placebo.

Table 23. Extent of Study Drug Exposure

Parameter	zolpidem SL 1.0-mg/1.75-mg	zolpidem SL 3.5-mg	placebo	Total
Total # of subjects who took ≥1 dose	130	436	315	585
Study ZI-05-009	24	24	24	24
Study ZI-06-010	82	80	81	82
Study ZI-12	0	150	145	295
Study ZI-13	0	36	0	36
Study ZI-14	24	47	0	48
Study ZI-15	0	34	0	34
Study ZI-16	0	29	30	30
Study ZI-17	0	36	35	36
Total # of study drug doses received				
1-4	130 (100%)	295 (67.8%)	144 (45.7%)	
5−10	0 (0.0%)	22 (5.0%)	53 (16.8%)	
11−20	0 (0.0%)	60 (13.7%)	58(18.4%)	
21−28	0 (0.0%)	59 (13.5%)	61(19.4%)	
Mean (SE)	2.2 (0.1)	7.2 (0.4)	10.1 (0.5)	
Median	2.0	2.0	8.0	
Cumulative dose of zolpidem SL (mg)				
Mean (SE)	3.6 (0.1)	25.1 (1.4)	NA	26.0 (1.4)
Median	3.5	7.0	NA	10.5
Range	1.8 to 5.5	3.5 to 98.0	NA	1.8 to 98.0
Duration of drug treatment (days)*				
Mean (SE)	2.2 (0.1)	9.6 (0.5)	13.0 (0.7)	
Median	2.0	2.0	6.0	
Range	1 to 4	1 to 28	1 to 28	

*: This is the total number of days that a subject was in the treatment phase of the study. In the parallel, double-blind, Study ZI-12, it is the last dose date minus the first dose date plus one in the double-blind treatment phase of the study. For the crossover studies, it is the sum of last dose date minus the first dose date plus 1 within each period. Source: Section 5.3.5.3.2, Table 2.1.

Since the ZI-12 trial is to be the basis for much of the safety labeling, exposure was analyzed in this trial individually (as well as in the pooled exposure). Table 24 presents the exposure data for the trial. Discussion of exposures by week is included in the analysis of dependency and abuse.

Table 24. Extent of Study Drug Exposure (Study ZI-12)

Parameter	**zolpidem SL 3.5 mg**	**Placebo**
Total Number of Subjects who took at least 1 dose[a]	150	145
Total Number of Study Drug Doses Received[b]		
1	1 (0.7%)	5 (3.4%)
2	4 (2.7%)	0 (0.0%)
3	2 (1.3%)	3 (2.1%)
4	2 (1.3%)	0 (0.0%)
5−10	22 (14.7%)	18 (12.4%)
11−15	32 (21.3%)	24 (16.6%)
16−20	28 (18.7%)	34 (23.4%)
21−25	28 (18.7%)	38 (26.2%)
26−28	31 (20.7%)	23 (15.9%)
Mean (SE)	17.4	17.9
Median	18.0	19.0
Range	1 to 28	1 to 28
Cumulative dose (mg) of zolpidem SL		
Mean (SE)	60.8 (2.2)	
Median	63.0	
Range	3.5 to 98.0	

Note: Percentages are out of the Safety Population.
a: This is equivalent to showing the total number of days of study drug treatment.
b: This is the total amount of active treatment received during the treatment phase of the study.
c: This is the total number of days that the subject was in the treatment phase of the study.
d: In this study, it is the last dose date minus the first dose date plus 1 in the double-blind treatment phase of the study. Source: Clinical Study ZI-12, Section 5.3.5.1.2

The trial allowed for as-needed (PRN) self-medication of the study drug. Review of the frequency with which the drug was used shows that it varies from 1 time during the entire 4-week trial to every night. Despite meeting the required frequency of use during the screening phase, 9/152 (6.0%) of the zolpidem-assigned subjects used the drug ≤ once per week during the active phase, with a similar finding in the placebo group (8/145, 5.5%). At the other end of the use spectrum, 31/152 (20.7%) of the zolpidem and 23/145 (15.9%) of the placebo groups took the assigned medication nearly every night.

Overall the mean frequency of use was 17.4 nights (i.e., the study drug was taken on 62.1% of the 28 possible nights) for the zolpidem group and 17.9 (64%) for the placebo group. The groups were very similar in their self-medication, which is rather surprising considering the length of the trial. Analysis of drug use by week, Section * affirms that use did not significantly decline in the placebo group, despite the lack of an active ingredient for their insomnia.

The other pivotal trial (ZI-06-010*)* was a cross-over design so for each subject the drug exposure was 2 doses each of zolpidem SL 1.75 mg, 3.5 mg and placebo.

Exposure to zolpidem tartrate SL 3.5 mg during the drug development phases and the pivotal trials in adults <65 years age is considered by this review to be sufficient.

7.2.2 Explorations for Dose Response

Rationale for dose selection was based on the ZI-05-009 PK/PD trial that evaluated the 1.0 mg, 1.75 mg, and 3.5 mg doses of zolpidem SL. The 1.0 mg dose did not achieve the PK levels, or show evidence of clinical changes, that justified use of the drug.

Dose response was demonstrated in the pivotal efficacy trials. ZI-06-010 showed a dose-response comparison of the 1.75 mg and 3.5 mg doses of zolpidem SL. The dose-to-dose comparisons did not always show statistical significance, but were consistent in showing a response difference to placebo and to each other. On the basis of the Phase 1 and Phase 3 trials, the sponsor proposes the zolpidem SL (b) (4)

(b) (4) For use in the elderly, the dose response for the 1.75 mg dose is based only on a PK trial. The sponsor relies on the previous use of Ambien® for elderly patients to supplement the safety profile.

7.2.3 Special Animal and/or In Vitro Testing

No animal or in-vitro testing was done in this NDA development program. The sponsor relies on the data supplied for the approved referenced parent drug Ambien®.

7.2.4 Routine Clinical Testing

The methods used by the sponsor for routine clinical testing were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor references the Ambien® Package Insert for drug-accumulation information. The sponsor states that in the Ambien® trials of 2-week duration accumulation was not evidenced, so there is no reason to assume that drug accumulation should pose a problem with the lower doses used in this submission since the elimination $T_{1/2}$ is unchanged. On this basis, the sponsor asserts that the distribution, metabolism and elimination kinetics of zolpidem SL does not differ from that of Ambien®. The data presented are not inconsistent with that claim although it is noteworthy that the drug-accumulation studies in the past have been conducted in the non-elderly population.

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

Since this is a 505(b)(2) application, the sponsor has not conducted any additional trials to address abuse and dependence for this zolpidem SL formulation. The Agency agreed Pre-NDA Meeting Minutes, May 01, 2008) to allow data from the referenced drug Ambien®, as presented in the package insert, to suffice.

The Schedule IV controlled substance sedative-hypnotics have a potential for abuse or dependence. The longest use presented with this application is the 4-week PRN dosing for Study ZI-12. There is no evidence of increased usage over the course of the trial. The follow-up was not adequate for any evidence of possible drug withdrawal or rebound effects.

The potential for illicit extraction of active ingredients is probably deterred by the lower doses available with the proposed formulations (compared to the referenced drug Ambien® and other sedative-hypnotics). The sponsor also asserts that the ingredients affecting solubility, such as the foamy effervence in liquids should prevent use in IV fluids or slipping a tablet into drinks.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the zolpidem tartrate SL clinical development program.

7.3.2 Nonfatal Serious Adverse Events

Only one SAE was reported during the clinical development program. It was in Study ZI-12 and classified as a psychiatric disorder, but the subject was still in the screening phase (placebo use) and had not yet received the study drug.

7.3.3 Dropouts and/or Discontinuations

Pivotal Trials:
There were no subject discontinuations in Study ZI-06-010. There was 1 discontinuation in ZI – 12, occurring in the placebo group, due to 2 AEs (headache and abdominal pain), and no discontinuations in the zolpidem group due to AEs. Another subject, in the placebo group with an AE of an ankle sprain, was listed in the data tabulations as discontinued, but final results for the correctly data end-of-trial showed the subject completed the trial.

Other Trials:
One subject in Study ZI-16 in the placebo group with an AE of sinus infection was discontinued. In Study ZI-17, a 23-year- old who had received zolpidem SL 3.5 mg was discontinued due to AEs of headache and strep throat; she was also noted to have an elevated CPK.

The sponsor supplied the following data on withdrawals and discontinuations from other zolpidem trials (trials not a part of the drug development for this NDA):

> *Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).*
>
> *Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).*
>
> *Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.*

7.3.4 Significant Adverse Events

During the pivotal trial ZI-12, there was only one withdrawal (Subject 14023) due to adverse events (2 events - abdominal pain and severe headache).

7.3.5 Submission Specific Primary Safety Concerns

Complex Behaviors During Sleep
The class of sedative-hypnotics, including the approved referenced drug Ambien®, recently underwent labeling changes due to concerns about confusional arousal states during sleep. Reports included activities such as sleep walking or driving, eating, talking on the telephone, sexual acts and other events for which the individuals have little or no subsequent recall. The occurrence of these events, labeled complex behaviors during sleep, appears to be more frequent with the use of sleeping medications.

The sponsor identified the following terms of AEs in this category which they included in their search of the pooled INDs: sleep walking, sleep talking, somnambulism, night terror, parasomnia, global amnesia, sleep eating, and sleep driving. The sponsor concluded that "no evidence was reported of parasomnias or complex abnormal behaviors during the nighttime trials or any similar reports (i.e., confusional states or abnormal actions other than lightheadedness/dizziness) in the daytime trials".

Since the incidence of such activities is infrequent, the trial exposures would not have been expected to elicit such reports. This review did not find evidence of specific actions, but does note that confusion and amnesia as general descriptive terms were reported.

Note: the sponsor used the term parasomnia defined as "an unpleasant or undesirable event or experience that occurs during sleep, which has been reported for oral zolpidem tartrate (Ambien® Package Insert)". According to the Dorlands' Medical Dictionary (26th edition p.968), parasomnia is "a state in which there is no response to stimuli, verbal or mental, except that of a reflex nature".

Oral Irritation and Gastrointestinal AEs

Since the proposed medication is formulated to start dissolving in the mouth, the Agency requested that oral inspection be included in the physical examinations. The investigators examined the subjects' mouths a few minutes after administration of any study drug in each of the trials except the "at home" trial (ZI-12) where oral examinations were done only during study visits. In the review, any reports (subject or investigator initiated) related to oral changes were included.

Overall, the groups receiving zolpidem had a higher reported rate of oral complaints compared to the placebo groups (2.3%, 1.8% and 0.6% for the 1.0/1.75 mg, the 3.5 mg zolpidem, and placebo, respectively). Stomatitis (oral inflammation) was infrequent, but reported only in

zolpidem-assigned subjects. (Table 25). The sponsor also supplied information on the administration of the zolpidem SL 5 mg and 10 mg. Some of the trials for the higher SL doses included longer requirements for holding the tablets in the mouth (up to 10 minutes), but did not evidence significant differences in oral inspections between placebo and zolpidem groups.

Table 25. Summary of TEAEs Related to Oral Irritation (Pooled 8 IND Studies)

MedDRA System Organ Class Preferred Term	**zolpidem SL 1.0/1.75 mg**	**zolpidem SL 3.5 mg**	**placebo**	**Total**
Number of Subjects	130	436	315	585
Number of Subjects with ≥1Reports of Oral Irritation	3 (2.3%)	8 (1.8%)	2 (0.6%)	12 (12.1%)
Oral Disorders Seen or Reported*				
Hypoesthesia Oral	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Oral Discomfort	1 (0.8%)	2 (0.5%)	0 (0.0%)	2 (0.3%)
Oral Disorder	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Oral Pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Paresthesia Oral	0 (0.0%)	3 (0.7%)	1 (0.3%)	4 (0.7%)
Stomatitis	2 (1.5%)	3 (0.7%)	0 (0.0%)	5 (0.9%)

* More than one disorder per subject may have been reported

Reviewing for treatment-attributable oral lesions in the Study ZI-12 listings showed the following: Subject 07008 with an oral lesion (2 mm oval white buccal mucosa lesion) on Visit 2 post-dosing, but apparently resolved by Visit 3 and the final visit. The lesion was not noted on the screening practice examination. Subject 2004 was noted to have 2 small petechia near the right 3rd molar on Visit 2 only. Subject 20100 was recorded as a normal oral screening exam, with periodontal disease of a lower incisor for all subsequent visits.

Two of the 3 cases had no reported evidence of oral changes at the final visit, and the third case can not be evaluated regarding chronic vs new onset, so this review does not find any substantial evidence of the sublingual tablet causing oral mucosal changes.

7.4 Supportive Safety Results

The majority of treatment-emergent AEs reported by subjects treated with zolpidem tartrate sublingual lozenge were mild in severity, with the exception of sedation and fatigue which were assessed as moderate in severity, and pharyngolaryngeal pain and headache which were assessed as severe. Of the TEAEs reported by subjects treated with placebo, 2 TEAEs of somnolence were assessed as mild, and an AE of muscle spasms was assessed as moderate in severity.

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events (TEAEs) in the pooled (8) IND Studies (Studies ZI-05-009, ZI-13, ZI-14, ZI-15, ZI-16, ZI-17, ZI-06-010, and ZI-12,) are represented in Table 26. The pooled safety data represents both cross-over and parallel trials, as well as varying lengths of exposure. Comparison of subjects reporting at least one TEAE (treatment emergent adverse event), shows the percentages are 26.1% for the zolpidem SL 3.5 mg group, 19.2% for the 1.0mg/1.75 mg group, and 17.1% for the placebo group.

In the zolpidem SL 3.5 mg group, the most common reported TEAEs (≥1%) were somnolence (6.2%), headache (5.5%), fatigue (2.3%), dizziness (2.3%), and nausea (2.1%). In the 1.0 mg/1.75 mg group, fatigue (9.2%), somnolence (5.4%), headache (3.1%), stomatitis (1.5%), and dizziness (1.5%) were most frequently reported. As the sponsor notes, most of the trials with the lower doses were daytime trials where a higher reporting of fatigue and somnolence would be expected.

The most common TEAEs (≥1%) reported by the placebo group were fatigue (1.9%), nasopharyngitis (1.6%), somnolence (1.6%), and nausea (1.0%).

Table 26. Summary of TEAEs (≥1%) by System Organ Class (SOC) and MedDRA Term (Safety Population – Pooled 8 INDs)

MedDRA System Organ Class Preferred Term	**zolpidem 1.0/1.75 mg**	**zolpidem 3.5 mg**	**Placebo**	**Total**
Number of Subjects	130	436	315	585
Number of Subjects Reporting at Least 1 Treatment-Emergent Adverse Event	25 (19.2%)	114 (26.1%)	54 (17.1%)	164 (28.0%)
Gastrointestinal Disorders	**4 (3.1%)**	**21 (4.8%)**	**12 (3.8%)**	**33 (5.6%)**
Nausea	0 (0.0%)	9 (2.1%)	3 (1.0%)	12 (2.1%)
Stomatitis	2 (1.5%)	3 (0.7%)	0 (0.0%)	5 (0.9%)
General Disorders and Administration Site Conditions	**12 (9.2%)**	**15 (3.4%)**	**6 (1.9%)**	**24 (4.1%)**
Fatigue	12 (9.2%)	10 (2.3%)	6 (1.9%)	19 (3.2%)
Infections and Infestations	**1 (0.8%)**	**8 (1.8%)**	**13 (4.1%)**	**22 (3.8%)**
Nasopharyngitis	0 (0.0%)	1 (0.2%)	5 (1.6%)	6 (1.0%)
Nervous System Disorders	**12 (9.2%)**	**61 (14.0%)**	**12 (3.8%)**	**77 (13.2%)**
Dizziness	2 (1.5%)	10 (2.3%)	1 (0.3%)	13 (2.2%)
Headache	4 (3.1%)	24 (5.5%)	2 (0.6%)	30 (5.1%)
Somnolence	7 (5.4%)	27 (6.2%)	5 (1.6%)	33 (5.6%)

Note 1: Adverse events were coded in accordance with the MedDRA thesaurus, version 10.1.
Note 2: Counts indicate the numbers of subjects in each group reporting one or more adverse events. For each level of summarization (system organ class, preferred term), subjects are only counted once. Percentages are based on the total number of subjects in the treatment group.
Note 3: Subjects for whom the AE worsened when starting a new treatment period were counted again under the new period. Source: ISS, Section 5.3.5.3.2

Study ZI-14

Safety results were reviewed more carefully in Study ZI-14 than the other non-pivotal trials since this was the only source for any data from elderly subjects. The AE profile was generally favorable for the zolpidem SL 1.75 mg and 3.5 mg use in the elderly cohorts, and there were no discontinuations due to AEs.

TEAEs (≥ 1 complaint) were reported by 2/24 (25.0%) of the elderly subjects receiving 1.75 mg zolpidem, by 13/23 (56.5%) of elderly subjects receiving the 3.5-mg dose, and by 18/24 (75.0%) of the non-elderly subjects on the 3.5 mg zolpidem dose.

All TEAEs reported by elderly subjects were mild or moderate, except for one subject with complaints of severe fatigue. Fatigue was reported by 3 elderly subjects in the low dose cohort,

by 4 elderly subjects on the 3.5 mg dose compared with none of the non-elderly subjects. By contrast, somnolence was not reported by any 1.75 mg treated elderly subjects, but was reported by 5 elderly subjects on the 3.5 dose, and by 11 of the non-elderly subjects. Since it can be difficult to distinguish between reports of fatigue and somnolence in insomnia trials, very little meaning can be ascribed to this discrepancy.

Of more clinical interest are the other AEs associated with the trial. Headache was reported by 2 and 3 elderly subjects treated with 1.75 mg and 3.5 mg zolpidem respectively, compared with 1 non-elderly subject. Dizziness was reported in 1 elderly subject treated with 1.75 mg, no elderly subjects treated with 3.5 mg, and 2 non-elderly subjects. Dysarthria, dysgeusia, and bronchial irritation, myalgia, and contusion (without report of a fall or precipitating event) were each reported in 1 elderly subject receiving zolpidem SL 3.5 mg, but not in the other cohorts. Table 27 shows the reports of AEs for the trial.

This review tried to evaluate the PK results for "outliers", such as those with longer T_{max} values, especially in the elderly cohort. There were no significant differences between the "outliers" and the other subjects in the AEs profile, lab values or EKGs. Subject No. 001-060 (AA018), age 74 years, received 3.5 mg zolpidem SL in the first leg of the crossover trial. He completed the trial, but was excluded from all PK analyses due to a pre-dose concentration higher than 5% of C_{max} despite a required 5-day washout before beginning the 1.75 mg leg of the trial. He had reported mild frontal headache during the trial (while on the 3.5 mg dose); no lab values were abnormal.

Table 27. Incidence of Treatment-Emergent Adverse Events by MedDRA – Study ZI-14

	Elderly			**Non-elderly**
MedDRA System Organ Class MedDRA Preferred Term	**1.75 mg n=24**	**3.5 mg N=23 n**	**All Subjects n=24 n**	**3.5 mg n=24**
Subjects with ≥ 1TEAE	6 (25.0%)	13 (56.5%)	16 (66.7%)	18 (75.0%)
Nervous system	3 (12.5%)	8 (34.8%)	10 (41.7%)	14 (58.3%)
Somnolence	0 (0.0)	5 (21.7%)	5 (20.8%)	11 (45.8%)
Headache	2 (8.3%)	3 (13.0%)	5 (20.8%)	1 (4.2%)
Dizziness	1 (4.2%)	0 (0.0)	1 (4.2%)	2 (8.3%)
Dysarthria	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Dysgeusia	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Depressed level of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Stupor	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
General and administration site conditions	3 (12.5%)	4 (17.4%)	6 (25.0%)	1 (4.2%)
Fatigue	3 (12.5%)	4 (17.4%)	6 (25.0%)	0 (0.0)
Feeling of relaxation	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Gastrointestinal	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3%)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3%)
Oral discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Injury, poisoning and procedural complications	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Contusion	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Musculoskeletal and connective tissue	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Myalgia	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Respiratory, thoracic and mediastinal	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Bronchial irritation	0 (0.0)	1 (4.3%)	1 (4.2%)	0 (0.0)
Psychiatric	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Skin and subcutaneous tissue	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2%)

Source: Clinical Study ZI-14, Section 16.2.7.1

TEAEs in the Pivotal Trials

Study ZI-06-010
A total of 15 of the 82 subjects (18.3%) reported AEs during the study, of which 12 are considered to have had possibly treatment-related AEs (TRAEs). For 3 subjects, the only during the screening period. AEs for 4 subjects occurred while in the 3.5 mg period, for 3 subjects during the 1.75 mg period, and for 7 subjects during the placebo period. All AEs were mild or moderate in severity. There were no SAEs or deaths reported during the study.

Table 28 is a summary of TRAEs by type of event. The case of glossodynia was rated as mild in severity, and resolved within 1 day.

Table 28. TRAEs Related to Study Drug – Trial ZI-06-010

System Class Preferred Term, n (%)	**3.5 mg**	**1.75 mg**	**Placebo**
Number of Patients	80	82	81
Number of Patients Reporting at Least 1 TRAE	1 (1.3%)	0 (0.0%)	4 (4.9%)
Gastrointestinal Disorders	1 (1.3%)	0 (0.0%)	1 (1.2%)
Glossodynia	1 (1.3%)	0 (0.0%)	0 (0.0%)
Oral Pain	0 (0.0%)	0 (0.0%)	1 (1.2%)
Nervous System Disorders	0 (0.0%)	0 (0.0%)	3 (3.7%)
Paraesthesia Mucosal	0 (0.0%)	0 (0.0%)	1 (1.2%)
Paraesthesia Oral	0 (0.0%)	0 (0.0%)	1 (1.2%)
Sedation	0 (0.0%)	0 (0.0%)	2 (2.5%)

Note: Counts indicate the number of patients reporting 1 or more events that map to the MedDRA system organ class. At each level of summarization (system organ class or preferred term), patients are only counted once.
Source: Study ZI-06-010, Section 12.2.2

In addition to the TRAEs, there were the following AEs:

- On 3.5 mg: one subject with increased blood pressure (also present during screening, but not while on other active drug phases)
- On 1.75 mg: one subject with a UTI and one positive for glucose in urine (not present during screening)
- On placebo: one subject with nausea, and one with diarrhea.

ZI-12

The sponsor has requested that the safety data from Study ZI-12 be used for the primary labeling safety data. The rationale is that the data reflects use of the drug under the expected conditions (home use, and on an as-needed basis) and provides evaluation of the drug over a longer time-frame (4-week trial). Subjects with multiple occurrences of the same events are only counted once within the same system organ class or preferred term.

During the screening phase/baseline of the study (placebo administration), the only Serious Adverse Event (SAE) for the trial occurred when 1 subject (0.1%) was withdrawn due to a hospitalization for a psychiatric disorder. Of the 403 subjects who were not randomized into the treatment phase of the study, 15 subjects (3.7%) experienced AEs that were similar in type and frequency to the AEs reported during the treatment phase.

As discussed previously, the only discontinuation (1 subject, 0.7%) during the active treatment phase of the trial was a subject in the placebo group with complaints of headache and abdominal pain.

A total of 71 AEs were reported during the 4-week active treatment period, with 57 subjects (19.3%) reporting at least 1 AE. All the TEAEs reported during the 4-week treatment phase are shown in Table 29. The most commonly reported TEAEs (>1% by treatment group) were headache (2.7%), nausea (1.3%), and fatigue (1.3%) in the zolpidem group. In the placebo group were reports of nasopharyngitis (3.4%), somnolence (1.4%), headache (1.4%), back pain (1.4%) and abdominal pain (1.4%).

Table 29. Summary of TEAEs (≥1%) by SOC and MedDRA Term – Study ZI-12 (Safety Population)

MedDRA System Organ Class Preferred Term	**zolpidem SL 3.5 mg (n=150)**	**placebo (n=145)**	**Total (n=295)**
# of Subjects Reporting ≥1 TEAE	29 (19.3%)	28 (19.3%)	57 (19.3%)
Gastrointestinal Disorders	**6 (4.0%)**	**3 (2.1%)**	**9 (3.1%)**
Abdominal Pain	1 (0.7%)	2 (1.4%)	3 (1.0%)
Nausea	2 (1.3%)	1 (0.7%)	3 (1.0%)
General Disorders and Administration Site Conditions	**5 (3.3%)**	**0 (0.0%)**	**5 (1.7%)**
Fatigue	2 (1.3%)	0 (0.0%)	2 (0.7%)
Infections and Infestations	**5 (3.3%)**	**10 (6.9%)**	**15 (5.1%)**
Nasopharyngitis	0 (0.0%)	5 (3.4%)	5 (1.7%)
Injury, Poisoning, and Procedural Complications	**2 (1.3%)**	**5 (3.4%)**	**7 (2.4%)**
Joint Sprain	0 (0.0%)	2 (1.4%)	2 (0.7%)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0%)**	**4 (2.8%)**	**4 (1.4%)**
Back Pain	0 (0.0%)	2 (1.4%)	2 (0.7%)
Nervous System Disorders	**7 (4.7%)**	**5 (3.4%)**	**12 (4.1%)**
Headache	4 (2.7%)	2 (1.4%)	6 (2.0%)
Somnolence	1 (0.7%)	2 (1.4%)	3 (1.0%)

Note 1: Adverse events were coded in accordance with the MedDRA thesaurus version 10.1.
Note 2: Counts indicate the numbers of subjects in each group reporting one or more adverse events. For each level of summarization (system organ class, preferred term), subjects are only counted once. Percentages are based on the total number of subjects in the treatment group.
Note 3: Subjects for whom the AE worsened when starting a new treatment period were counted again under the new period. All subjects were 18 to 64 years of age in this study.
Source: Study ZI-12, Section 5.3.5.3.2,

This review also compared the findings discussed above to the TEAEs profile used in labeling by the approved parent drug Ambien® (Table 30). The most commonly observed adverse reactions, compared to placebo, in controlled trials during short-term treatment (up to 10 nights) with Ambien® (doses up to 10 mg), were drowsiness (2%), dizziness (1%), and diarrhea (1%).

Table 30. Incidence of TEAEs in Placebo-Controlled Clinical Trials Lasting up to to 10 Nights (Percentage of patients reporting)

Body System Adverse Event	Zolpidem (1.25 to 10 mg) (n=685)	Placebo (n=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	-

Source: Ambien Package Insert * Reactions reported by at least 1% of patients treated with Ambien and at a greater frequency than placebo.

The most commonly reported adverse events during longer-term treatment with Ambien® at doses up to 10 mg (compared to placebo-treated patients) were dizziness (5%) and drugged feelings (3%) (Table 31). The Ambien® labeling data is based on trials of 28 to 35 nights duration.

Table 31. Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials Lasting 28 to 35 Nights

Body System/Adverse Event*	**Zolpidem (5 or10 mg) (n=152)**	**Placebo (n=161)**
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central & Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethary	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnorrnal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-
Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

* Reactions reported by at least 1% of patients treated with Ambien and at a greater frequency than placebo
Source: Ambien® label

The majority of treatment-emergent AEs reported by subjects treated with zolpidem tartrate sublingual lozenge were mild in severity. Other than sedation or fatigue (rated "moderate" in severity), only pharyngolaryngeal pain (1) and headache (1) were rated as severe. Subjects treated with placebo reported TEAEs of "mild" somnolence (2), and "moderate" muscle spasms (1).

7.4.2 Laboratory Findings

Drug-Laboratory Test Interactions

The sponsor relies on the reference drug, oral Ambien®. According to the Ambien® Package Insert, the drug is not known to interfere with commonly employed clinical laboratory tests, or to cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

CLINICAL LABORATORY EVALUATIONS

Review of laboratory tests of hematology, serum chemistry, and urinalysis was conducted for all 8 individual INDs in a check of the pooled INDs safety data. The review used only the end-of-trial lab values compared to the screening/baseline values. Testing generally included alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase, gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), serum electrolytes, and albumin. Overall, there were few significant changes in lab values compared to baseline values. Of the changes noted, occurrences were as frequent in the placebo groups as in the active treatment groups. The lack of findings is probably not surprising since until the Phase 3 trials, subjects generally had only single-dose exposures and lab testing concluded shortly after exposures.

In Study ZI-12, where lab testing was performed over a 4-week period of exposure, three female subjects had decreased bilirubin (2 treated with zolpidem, and 1 treated with placebo). One male, and 2 females treated with zolpidem, and 1 male treated with placebo had decreased glucose at end of study. None of the changes were clinically significant.

7.4.3 Vital Signs

Vital signs collected during the trials usually included systolic/diastolic blood pressure, heart rate, oral temperature, and respiratory rate. The sponsor states that because vital signs were not collected at consistent time points across all eight IND studies, the submitted data focused on changes from baseline to the 4-hour post-dose.

Review of the vital signs did not show any significant changes, or suggestive patterns. One of the shortcomings of this NDA submission is the lack of vital signs information that would correspond to changes that might occur during the period the medication is presumed to be most active. Systematic monitoring for possible orthostatic hypotension have not been done during the drug development for this formulation, or for the parent drug Ambien®.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was usually conducted at screening, not all trials repeated the ECG at the end-of-treatment visit or early discontinuation.

The majority of abnormal findings were not clinically significant, and most occurred in the screening (with normalization on end-of-trial in studies that repeated ECG).

In Study ZI-12, a female subject (16031) had ECG changes recorded as a possible anterior wall infarct (age unknown). She was reported as having no symptoms at the final visit, and was lost to follow-up.

7.4.5 Special Safety Studies/Clinical Trials

Study ZI-14 -
Zolpidem tartrate SL was studied at doses of 1.75 mg and 3.5 mg in a daytime dosing study in 24 healthy geriatric (65 to 83 years) volunteers and 24 younger adult (< 65 years) healthy volunteers. Overall, 25% of 1.0 mg/1.75 mg treated and 56% of 3.5 mg zolpidem -treated elderly subjects experienced ≥1 TEAE compared with 75% of adult, non-elderly subjects treated with the 3.5 mg dose. When compared to the younger subjects, the elderly subjects did not show an increased AE incidence, or any difference in the type AEs reported.

The 1.75 mg zolpidem showed dose-proportional PK parameters when compared to the 3.5 mg dose in elderly subjects. At the 1.75 mg dose in elderly subjects, the corresponding values of Cmax and AUC were consistently lower than those observed with zolpidem tartrate sublingual lozenge, 3.5 mg, in younger cohorts and consistently higher than the 1.75 mg dose. There was no significant change in the elimination half-life ($t_{1/2}$) with comparison of the elderly and non-elderly groups. Oral clearance was reduced by 24% in the elderly subjects on the lower dose..

7.4.6 Immunogenicity

No data on immunogenicity was submitted for this NDA. The sponsor relies on the data generated for the approved parent reference drug Ambien®.

7.5 Other Safety Explorations

Assessment of Morning Sleepiness/Alertness, Possible Effects on Driving, and Dosing too Late or Multi-dosing are reviewed in Section 7.7.

7.5.1 Dose Dependency for Adverse Events

Also discussed in Section 7.4.1. The dose dependency for adverse events is summarized in Table 32.

The frequency of AEs between the 1.0/1.75 mg., 3.5 mg, and placebo treatment groups shows a small and consistent dose-dependent relationship. An exception is the higher frequency of AEs reported in the lowest dose group (1.0 mg/1.75 mg) in the early-phase daytime trials when

compared to the 3.5 mg group. The sponsor considered the finding an artifact due to the small number of subjects exposed to the low doses which is probably accurate. Overall, the frequency of AE complaints of headache (5.5%) and dizziness (2.3%) were higher with the 3.5 mg dose. The frequency of AEs in the Phase 3 Study ZI-06-010, which administered both high and low dose strengths, was similar to the previous trials except that complaints of somnolence and fatigue were higher in the daytime trials.

Table 32. Summary of TEAEs (≥1%) by SOC and MedDRA Term (All Eight INDs)

MedDRA System Organ Class Preferred Term	**1.0 mg/ 1.75 mg zolpidem**	**3.5 mg zolpidem SL**	**Placebo**	**Total**
Number of Subjects	130	436	315	585
# of Subjects Reporting ≥1 TEAE	25 (19.2%)	114 (26.1%)	54 (17.1%)	164 (28.0%)
Gastrointestinal Disorders	**4 (3.1%)**	**21 (4.8%)**	**12 (3.8%)**	**33 (5.6%)**
Nausea	0 (0.0%)	9 (2.1%)	3 (1.0%)	12 (2.1%)
Stomatitis	2 (1.5%)	3 (0.7%)	0 (0.0%)	5 (0.9%)
General Disorders & Administration Site Conditions	**12 (9.2%)**	**15 (3.4%)**	**6 (1.9%)**	**24 (4.1%)**
Fatigue	12 (9.2%)	10 (2.3%)	6 (1.9%)	19 (3.2%)
Infections and Infestations	**1 (0.8%)**	**8 (1.8%)**	**13 (4.1%)**	**22 (3.8%)**
Nasopharyngitis	0 (0.0%)	1 (0.2%)	5 (1.6%)	6 (1.0%)
Nervous System Disorders	**12 (9.2%)**	**61 (14.0%)**	**12 (3.8%)**	**77 (13.2%)**
Dizziness	2 (1.5%)	10 (2.3%)	1 (0.3%)	13 (2.2%)
Headache	4 (3.1%)	24 (5.5%)	2 (0.6%)	30 (5.1%)
Somnolence	7 (5.4%)	27 (6.2%)	5 (1.6%)	33 (5.6%)

Note 1: Adverse events were coded in accordance with the MedDRA thesaurus, version 10.1.
Note 2: Counts indicate the numbers of subjects in each group reporting one or more adverse events. For each level of summarization (system organ class, preferred term), subjects are only counted once. Percentages are based on the total number of subjects in the treatment group.
Note 3: Subjects for whom the AE worsened when starting a new treatment period were counted again under the new period.
Source: SSI, Section 5.3.5.3.2

7.5.2 Time Dependency for Adverse Events

Residual Effects

Additional discussion of possible residual effects for the pivotal trials is in Section 7.4.1.

The sponsor, Transcept conducted a search of the MedDRA system organ class (SOC) categories to elicit any evidence suggestive of residual effects. The categories search was quite broad-based and inclusive. During the safety review, the reports of AEs from all the trials included in the safety review were searched and analyzed for frequency, patterns, unique cases of interest, and where possible, relationship to PK data as well as dose strength. Searching of the AEs by trial did not elicit any new findings, although a few were mislabeled as to whether the subjects completed the trial, and several lacked information on the duration of the AE symptoms. None of these were enough to cause a change in the statistics or conclusions.

AEs in pre-dosing periods, and in subjects receiving placebo were collected for comparison information, but the focus was on subjects receiving active drug treatment. For the residual effects assessment, relationship of the AE complaint to the timing of the drug administration was included when the information was available. Most of the daytime trials showed AE reports closely following administration of the drug. The pivotal trials were the only ones to provide a source for AEs reported on awakening.

Table 33 provides a summary of TEAEs with possible association with residual effects. The overall distribution of TEAEs that could be associated with residual effects was similar between the treatment groups..

Table 33. Summary of Treatment-Emergent Special-Interest Adverse Events: Possible Residual Effects by System Organ Class and MedDRA Term in Group 1 (All Studies ZI-05-009, ZI-06-010, ZI-12, ZI-13, ZI-14, ZI-15, ZI-16, and ZI-17)

MedDRA System Organ Class Preferred Term	**1.0-mg/1.75-mg zolpidem SL**	**3.5-mg zolpidem SL**	**Placebo**	**Total**
Number of Subjects	130	436	315	585
# Subjects Reporting ≥1 Residual Effect Adverse Event	18 (13.8%)	50 (11.5%)	15 (4.8%)	64 (10.9%)
Eye Disorders	**1 (0.8%)**	**3 (0.7%)**	**0 (0.0%)**	**4 (0.7%)**
Vision Blurred	1 (0.8%)	3 (0.7%)	0 (0.0%)	4 (0.7%)
General Disorders and Administration Site Conditions	**12 (9.2%)**	**10 (2.3%)**	**6 (1.9%)**	**19 (3.2%)**
Fatigue	12 (9.2%)	10 (2.3%)	6 (1.9%)	19 (3.2%)
Feeling Abnormal	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Nervous System Disorders	**8 (6.2%)**	**38 (8.7%)**	**8 (2.5%)**	**47 (8.0%)**
Somnolence	7 (5.4%)	27 (6.2%)	5 (1.6%)	33 (5.6%)
Dizziness	2 (1.5%)	10 (2.3%)	1 (0.3%)	13 (2.2%)
Sedation	0 (0.0%)	1 (0.2%)	2 (0.6%)	3 (0.5%)
Stupor	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Psychiatric Disorders	**0 (0.0%)**	**2 (0.5%)**	**1 (0.3%)**	**3 (0.5%)**
Confusional State	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Daydreaming	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Disorientation	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)

Note 1: Evidence suggestive of residual effects after MOTN dosing including the following SOC (PTs): Eye Disorders (nystagmus, vision blurred, vision impaired); General Disorders and Administration Site Conditions (asthenia, fatigue, feeling abnormal, feeling drug, lethargy, malaise, somnolence); Injury, Poisoning, and Procedural Complications (falls); Nervous System Disorders (amnesia, dizziness, drowsiness, memory impairment, sedation, slurred speech, stupor, unsteady gait, vertigo); Psychiatric Disorders (drugged feeling, confusion, confusional state, daydreaming, disorientation, dissociation, disturbance in attention, impaired concentration, inappropriate affect, mental impairment, mood altered); Respiratory, Thoracic, and Mediastinal Disorders (slowed respiration); and Vascular Disorders (orthostatic hypotension, syncope).
Note 2: Adverse events were coded in accordance with the MedDRA thesaurus, version 10.1.
Note 3: Counts indicate the numbers of subjects in each group reporting one or more adverse events. For each level of summarization (system organ class, preferred term), subjects are only counted once. Percentages are based on the total number of subjects in the treatment group.
Note 4: Subjects for whom the AE worsened when starting a new treatment period were counted again under

the new period. Source: ISS, Section 5.3.5.3.2

Responses to the Morning Sleepiness/Alertness questions and VAS ratings were used in the pivotal trials to determine possible residual effects of the drug. Results are discussed in more detail in Section 7.7 (Safety Issues).

7.5.3 Drug-Demographic Interactions

Elderly
By inclusion criteria, all subjects in the two pivotal trials were less than age 65 years.

Safety in the elderly subjects has been discussed above in the review of Study ZI-14, a daytime PK trial of elderly and non-elderly subjects. The safety outcomes of this study are discussed in Section 7.4.1. The elderly subjects received zolpidem SL 1.75 mg. and 3.5 mg in a cross-over trial, while the non-elderly adults received only the zolpidem SL 3.5 mg. dose.

Overall, the incidence of AEs was higher with the 3.5 mg dose than with the 1.75 mg dose of zolpidem tartrate sublingual lozenge. Fatigue and headache occurred more frequently in elderly than non-elderly subjects, regardless of dose. Complains of somnolence and dizziness were more frequently in the non-elderly cohort. The overall safety profile is consistent with other daytime administration studies, and does not raise specific concerns for use in the elderly at the recommended dose of 1.75 mg.

The following is extracted from the label of the reference drug, Ambien® which carries recommendations for use of the 5 mg dose for elderly patients.

> ***Geriatric use***
>
> *A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥ 60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤ 10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).*

Frequency of TEAEs in Elderly Subjects (>65 years) - Ambien® label

Adverse Event	Zolpidem ≤ 10 mg.	Placebo
Dizziness	*3%*	*0%*
Drowsiness	*5%*	*2%*
Diarrhea	*3%*	*1%*

> *A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses > 10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem*

reported confusion, including 18/24 (75%) who were ≥ 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses > 10 mg.

*The dose of Ambien® in elderly patients is 5 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see **WARNINGS and PRECAUTIONS**].*

Gender

In both of the pivotal trials, the majority of the subjects were females, 58/82 (71%) in Study ZI -06-010, and 186/274 (68%) in Study ZI-12. Statistical analysis the primary endpoint by gender for each trial indicated that there were no statistically significant differences between the genders (p=0.33 in ZI-06-010 and p=0.768 for ZI-12).

This review also compared gender differences in the reporting of AEs for all 8 INDs pooled as well as for the two pivotal trials.

Overall rate of subjects with ≥1 TEAE (≥1%):

1.0 mg/1.75 mg zolpidem group: females 15.9% vs males 21.6%
3.5 mg zolpidem group: females 21.2% vs males 18.1%
Placebo group: females 16.2% vs males 18.5%

The most commonly reported TEAEs (≥1%) in females vs males, respectively:

1.0 mg/1.75 mg zolpidem SL group: fatigue (5.8% vs 13.5%), somnolence (5.8% vs 8.1%), stomatitis (2.9% vs 0.0%), and headache (1.4% vs 2.7%).

3.5 mg zolpidem SL group: headache (3.9% vs 2.6%), dizziness (3.4% vs 0.0%), nausea (3.0% vs 0.9%), somnolence (3.0% vs 4.3%), fatigue (1.5% vs 2.6%), and vision blurred (0.5% vs 1.7%)

Placebo group: somnolence (1.6% vs 1.6%), fatigue (1.0% vs 3.2%), nasopharyngitis (1.0% vs 2.4%), and nausea (0.5% vs 1.6%)

The main difference between the groups appears to be the increase in headache, dizziness, and nausea for females in the zolpidem SL 3.5 mg group. Men tended to have more frequent complaints of fatigue and somnolence compared to women in all groups (i.e., daytime and nighttime trials).

There were no significant differences between what was observed overall and that observed for Study ZI-12. The TEAE profile appeared similar in males and females.

Race

In Study ZI-06-010, 51% were Caucasian, 44% Black, and 5% Other (Hispanic, Asian or Pacific) by classification. In Study ZI-12, 64% were Caucasian, 31% Black, and 4% Other.

In each trial, the changes in the primary endpoint analyzed by gender did not show statistically significant differences (p=0.41 for ZI-06-010, and p=0.11 for ZI-12. In the latter trial, the Other group had a higher LSO_{MOTN} (56.9 min.) compared to the Caucasian or Black groups (35.2 min. and 37.8 min., respectively). No generalizations could be made on the difference since such a small number of subjects were included in the group, so the difference was probably just an anomaly.

In the AEs review of all 8 INDs (pooled):

Overall rate of subjects with ≥1 TEAE (≥1%):

1.0 mg/1.75 mg zolpidem group: Caucasian 13.2% vs non-Caucasian 22.6%
3.5 mg zolpidem group: Caucasian 20.3% vs non-Caucasian 19.7%
Placebo group: Caucasian 20.5% vs non-Caucasian 12.0%

The most commonly reported TEAEs (≥1%) in Caucasian vs non-Caucasian, respectively:

Overall, a greater number of non-Caucasian than Caucasian subjects treated with 1.0-mg/1.75-mg zolpidem tartrate sublingual lozenge experienced an AE.

1.0 mg/1.75 mg zolpidem SL group: somnolence (7.5% vs 5.7%), fatigue (3.8% vs 13.2%), and headache (3.8% vs 0%)

3.5 mg zolpidem SL group: headache (3.6% vs 3.1%), somnolence (2.6% vs 4.7%), fatigue (0.5% vs 4.7%), dizziness (1.6% vs 3.1%), and nausea (1.6% vs 3.1%)

Placebo group: nasopharyngitis (2.6% vs 0.0%), somnolence (1.6% vs 1.6%), fatigue (1.1% vs 3.2%), and nausea (0.5% vs 1.6%)

This incidence of reported TEAEs was higher in the non-Caucasian subjects for the 1.0 mg/1.75 mg dose, but not for the 3.5 mg dose. Race/ethnic differences in reported TEAEs do not appear to be dose related.

There were no significant differences between what was observed overall and that observed in the pivotal trials.

7.5.4 Drug-Disease Interactions

As per Agency agreement, the sponsor relies on the reference drug, Ambien® Package Insert. For additional details see Use in Patients with Concomitant Illnesses (Section 7.5.5). The sponsor does recommend that zolpidem tartrate SL dose should be reduced to 1.75 mg in patients with hepatic insufficiency. Dose adjustment may not be necessary in patients with compromised renal function, but as a general precaution, close monitoring is recommended.

7.5.5 Drug-Drug Interactions

For each of the topics in this section, the sponsor has not conducted specific drug interaction studies as per Agency agreement, EOP2 Meeting Minutes, February 07, 2007, and pre-NDA Meeting Minutes, May 01, 2008). This is based on the sponsor's assertion that a change in the formulation and route of administration should not alter the metabolic pathway of zolpidem. Since it is a 505(b)2 application, it relies on the same recommendations and cautions as Ambien® for co-administration with other drugs.

Central Nervous System-Active Drugs
The package insert of the reference drug Ambien® contains the following sections on drug interactions:

> *Since the systematic evaluations of zolpidem in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.*
>
> *Ambien® was evaluated in healthy subjects in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.*
>
> *An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated [see **WARNINGS and PRECAUTIONS**].*
>
> *A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.*
>
> *Following five consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem Cmax was significantly higher (43%) and Tmax was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.*

Drugs That Affect Drug Metabolism Via Cytochrome P450
The package insert of the reference drug, Ambien®, contains the following sections on drug interactions affecting Cytochrome P450:

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes has not been carefully evaluated.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem tartrate (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in AUC0-∞ of zolpidem. There were no significant PD effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female volunteers between five consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem tartrate (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the area under the curve (AUC) (−73%), Cmax (−58%), and terminal elimination half-life (t1/2)(−36%) of zolpidem together with significant reductions in the PD effects of zolpidem.

A randomized, double-blind crossover interaction study in twelve healthy subjects showed that co-administration of a single 5 mg dose of zolpidem tartrate with ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem by a factor of 1.3 and increased the total AUC of zolpidem by a factor of 1.7 compared to zolpidem alone and prolonged the elimination half-life by approximately 30% along with an increase in the PD effects of zolpidem. Caution should be used when ketoconazole is given with zolpidem and consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together. Patients should be advised that use of Ambien® with ketoconazole may enhance the sedative effects.

Use in Patients with Concomitant Illnesses

The package insert of the reference drug, Ambien®, contains the following sections on use of zolpidem in patients with concomitant illness:

Clinical experience with oral zolpidem in patients with concomitant systemic illness is limited. Caution is advisable in using zolpidem tartrate sublingual lozenges in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of oral zolpidem in normal subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with Ambien® (10 mg) when compared to placebo. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be taken if zolpidem is prescribed to patients with compromised respiratory function.

Post-marketing reports of respiratory insufficiency, most of which involved patients with preexisting respiratory impairment, have been received. Zolpidem should be used with caution in patients with sleep apnea syndrome or myasthenia gravis.

Use in Subjects with Depression
The package insert of the reference drug, Ambien®, contains the following sections on the use of zolpidem by patients with depression:

As with other sedative/hypnotic drugs, zolpidem should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional over-dosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity, mutagenesis, and impairment of fertility

There is no information on human carcinogenicity, mutagenesis or impairment of fertility. The following non-clinical toxicology text is provided by the approved Ambien® package insert.

Carcinogenesis

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

Mutagenesis

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

Impairment of fertility

In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the

recommended human dose in mg/m². No effects on any other fertility parameters were noted.

7.6.2 Human Reproduction and Pregnancy Data

The following text is provided by the approved Ambien® package insert:

Pregnancy Category C

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

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

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

Labor and delivery

*Ambien has no established use in labor and delivery [see **Pregnancy**].*

Nursing mothers

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

7.6.3 Pediatrics and Assessment of Effects on Growth

Zolpidem tartrate is not indicated for use in pediatric patients. Based on trial data (8-week) of 201 children (aged 6-17 years) with attention-deficit hyperactivity disorder (ADHD), zolpidem (5mg and 10 mg) was ineffective for decreasing latency to sleep onset, and potentially unsafe with increased dizziness (23.5%), headache (12.5%) and hallucinations (7.4%) in the pediatric population(compared to 1.5%, 9.2%, and 0% respectively in adult patients). Ten subjects in the zolpidem groups (7.4%) discontinued or withdrew due to adverse events. The sponsor has requested a waiver from carrying out additional pediatric studies. We have requested that the sponsor consider pediatric trials to determine whether there may be efficacy and a safer risk profile for pediatrics with the lower sublingual dose of zolpidem. The drug presents the possibility of avoiding prophylactic use for insomnia since it can be used only when insomnia occurs, and the smaller concentration levels present less risk for morning residuals, both of which could be beneficial for pediatric use.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
Overdose was not reported in any of the clinical trials with zolpidem tartrate sublingual tablets.

The sponsor cites a review of 344 cases of intentional overdose (Garnier, 1994) in which acute overdose with zolpidem was considered "generally benign and requires no specific therapeutic measures beyond maintaining an airway and supporting ventilation and circulation, as for all sedative drug overdoses". Cases of serious complications due to zolpidem overdose nearly always included other medications that could explain respiratory failure. Review of literature revealed only one case attributed to zolpidem overdose (non-fatal) without confounding drugs, and the hypoxia reversed with oxygen via mechanical ventilation (Hamad, 2001).

The Ambien® Package Insert states:

> *In postmarketing experience of overdose with oral zolpidem tartrate alone, or in combination with central nervous system (CNS)-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise and fatal outcomes have been reported*.

Rebound Effect:
No trial designs for this NDA included assessment of the potential for rebound effect.

In the Ambien® label:

> ***Withdrawal effects***

*Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs [see **Drug Abuse and Dependence**].*

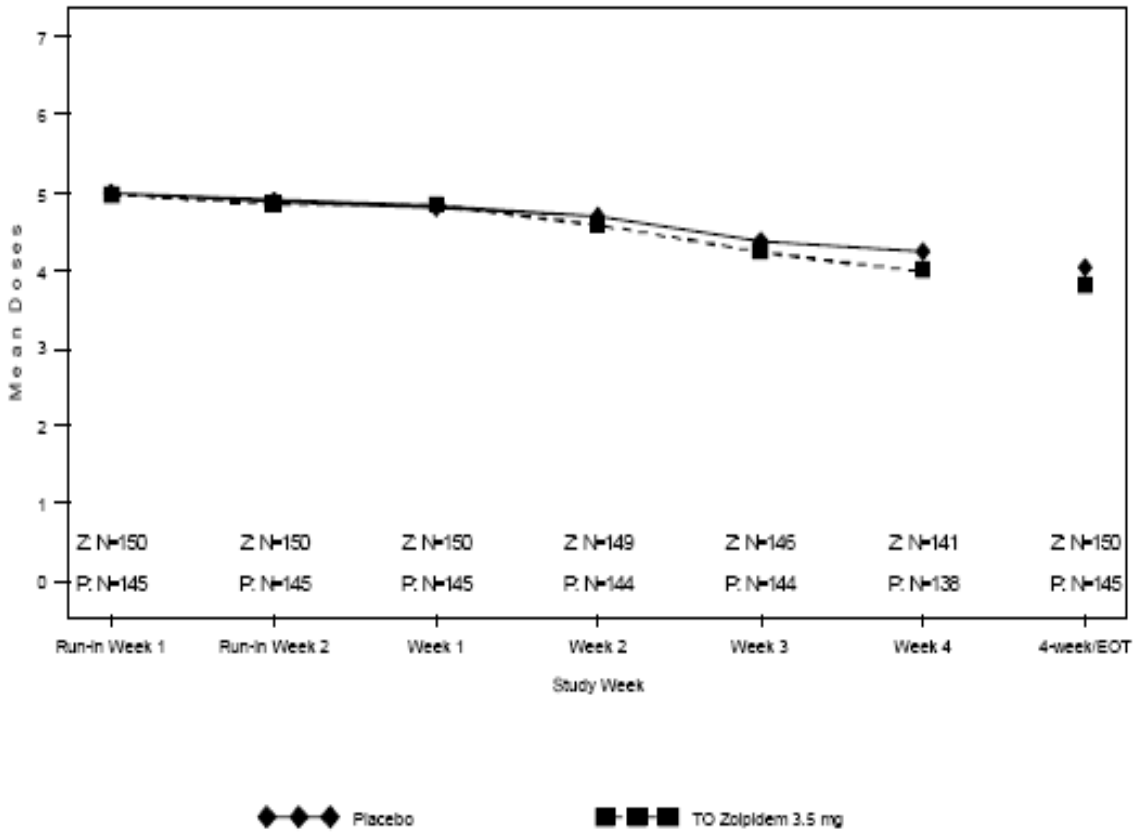
Adverse Events That Could Be Related to Abuse Potential or Dependence:
Transcept has not conducted any clinical evaluations of abuse potential with this drug.

Evaluating the potential for abuse or dependence in the pivotal trials, the sponsor presented, in the ISS, the result of MedDRA PTs mapping for all 8 INDs based terms from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for the evaluation of substance abuse (DSM-IV, Substance Abuse).

In the longest duration study conducted by Transcept, ZI-12, patients self-administered drug in the outpatient setting in response to spontaneous middle of the night awakenings. A review of Study ZI-12 revealed no evidence of events associated with abuse potential or dependence (withdrawal) effects. Additionally, it was shown that there was no increase in utilization in either active or placebo group during the 4-week treatment period of Study ZI-12 (see Section 1.2.2). The rate of use and change across time were comparable to the placebo group.

The number of doses of study medication taken during each treatment week is presented in Fig. 16. At Week 1, 150 subjects self administered zolpidem SL 3.5 mg, and 144 took placebo (p=0.309). Week 4 showed a decline in use, in the zolpidem-assigned group, 129 subjects reported use of the study drug, compared to 131 in the placebo group (p=0.255). There was no increase in utilization by either group over the 4weeks of the trial.

Fig. 16. Exposure by Treatment Week (Safety Population) – ZI-12



Source: Study ZI-12, Section 12.2

The zolpidem tartrate sublingual tablet is a Schedule IV controlled substance, and the sponsor has submitted a report on the potential of the drug for abuse, including the ease of synthesis, availability of precursor materials, difficulty of extraction, vaporization potential, solubilization potential for intravenous (IV) administration, potential for intranasal administration, and product tampering (in the ABL-001 Abuse Liability Assessment of Zolpidem Tartrate Sublingual lozenge, 1.75 mg and 3.5 mg.). The sponsor feels that unique product characteristics, including colorant, *in vitro* solubility, and effervescing excipients help prevent the inappropriate use of the product.

MedWatch review (adverse events reports to FDA AERS database) for a 10 year the period ending December 2007 revealed a total of 27, 239 spontaneous reports. There were 143 reports of dependence, 9 reports of addiction, 241 reports of abuse, and 158 reports of withdrawal where zolpidem was the primary/secondary suspect. Zolpidem was listed as the primary or secondary suspect for the following reports: euphoria/dysphoria (28), hallucination (478), or amnesia (999). Causality is difficult to assign, since many cases involved use of concomitant medications. The sponsor states that annual number of zolpidem tartrate prescriptions as of 2007 is (b) (4)

Reviewer's Comments
No data exists on the potential for the types of occurrences discussed above with zolpidem tartrrate SL 3.5 mg and 1.75 mg. However, due to the lower dose strengths, the potential for abuse, overdose and rebound effects would appear to be no higher (and probably lower) than with the referenced drug Ambien®.

7.7 Additional Submissions / Safety Issues

Residual Sedation and Alertness
As part of the safety evaluation, measurements of residual sedation were reviewed. A self-assessment using the Morning Visual Analog Scale (VAS) of Alertness, and the Digit Symbol Substitution Test (DSST) were done by subjects 30 minutes after the morning wake-up (4.5 hrs post-dose) in Study ZI-06-010. The differences between zolpidem SL 3.5 mg or 1.75 mg compared to placebo were virtually unchanged for either measurement (Table 34 and Table 35). For the VAS, there was a "placebo effect" of ~ 8 points on the 100 mm scale between the screening phase score and the placebo group score. The screening phase score was 3 points higher after the second night in the sleep lab, but the subsequent scores were stable. The DSST score improved ~ 3 points on the second day of the screening phase, probably due to a repetition effect, then remained stable for all groups. There were no significant differences in scores of the VAS or DSST comparing either dose of zolpidem to placebo.

Table 34. Morning Visual Analog Scale Self-Assessment (VAS) of Alertness – ZI-06-010

Parameter: VAS	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**
Mean Days 1 and 2, Post MOTN Awakening				
N	82	80	82	81
Mean (SEM)	55.7 (2.5)	63.6 (2.5)	64.2 (2.2)	62.4 (2.2)
Median	54.0	66.5	63.2	65.5
Min, Max	7.5, 97.5	12.0, 98.5	18.5, 99.5	21.5, 99.5
ANCOVA Analysis				
LS Mean		58.9	60.7	59.1

Source: modified from Study ZI-06-010, Section 12.5.3

Table 35. Morning Digit Symbol Substitution Test (DSST) Results – ZI-06-010

Parameter: DSST	**Screening**	**3.5 mg**	**1.75 mg**	**Placebo**
Mean Days 1 and 2, Post MOTN Awakening				
N	82	80	82	81
Mean (SEM)	58.2 (1.6)	60.6 (1.5)	61.6 (1.5)	61.9 (1.5)
Median	59.5	62.0	63.0	62.5
Min, Max	25.5, 93.0	27.0, 100.0	31.5, 92.5	28.0, 94.0
ANCOVA Analysis				
LS Mean		60.8	61.6	61.9

Note: Patient 215 was randomized to receive treatment A at Visits 6 and 7. However, treatment C was given both nights. Patient 211 was randomized to receive treatment B at Visits 8 and 9. However, treatment C was given at Visit 8 and treatment B was given at Visit 9. As a result, Patient 215's Visit 6 and 7 data and Patient 211's Visit 8 and 9 data are not included in the summaries. Source: modified from Study ZI-06-010, Section 12.5.3

In Study ZI-12, subjects were asked about next-morning residual effects on all mornings (within 30 minutes of awakening), regardless of whether study drug was taken the previous night. Morning Sleepiness/Alertness was assessed on a 9-point sleepiness scale (1="very sleepy" to 9=very awake and alert"). Subjects assigned to zolpidem reported statistically significant higher scores than the placebo group (p=0.0041) after nights that the drug was used. Baseline LS mean scores were 4.90 and 4.72 for the zolpidem and placebo groups, respectively. Post-dosing LS mean scores were 5.45 and 5.21, respectively. The treatment–attributable difference in the scores of 0.06 gave a p=0.0261 favoring zolpidem, but it can't be considered significant when the shift in scores from baseline was so small. Being "very awake and alert" should be the ideal goal of using a medication to improve sleep, but most subjects did not choose that description to characterize their next-morning experience.

Conclusions and Comments:
The DSST and VAS (Study ZI-06-010), and the Morning Sleepiness/Alertness Questionnaire (Study ZI-12) were the only assessments of residual effects. Although no significant differences were shown, or reported, these may not be the best indicators for use. As discussed previously when the endpoints for these measurements were discussed, post-sedative use may have a clouding effect on subjective reporting, and the DSST may not be sufficiently sensitive to changes in psychomotor performance. There was no assessment of reflexes, postural stability, driving, sustained attention or cognitive skills, or possible "late-day slump" with fatigue or decreased alertness, all of which should also be areas of concern in a safety review.

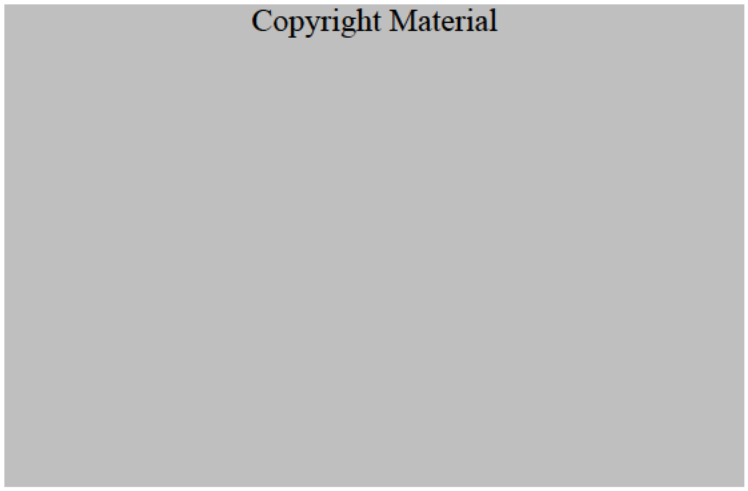
Comparison of zolpidem SL 3.5 mg to Ambien® 10 mg for Residual Effects and Possible Effects on Driving

No driving or simulated driving studies were conducted for this NDA for the evaluation of residual effects. A literature review was done to try to arrive at an estimate of the drug effect on driving and other early morning skills.

A recent placebo-controlled trial (Leufkens, 2009) included middle-of-the night administration of Ambien® 10 mg administered at 4:00 am, with subsequent return to sleep. Testing of cognition and psychomotor performance was conducted ~ 4.5 to 5.5 hours post-dose, and driving performance 5-6 hours post-dose. The residual effects were measured by the highway driving test included a 100 km (61 miles, ~ 1 hour) circuit requiring constant speed and steady lateral position (SDLP) with a specially instrumented vehicle and driving instructor. The driving evaluation was supplemented with lab tests of skills related to driving. These included the critical tracking test (CTT), and divided attention task. Cognitive testing included the DSST, and the word learning test. Postural stability was evaluated by measurement of body sway using a force platform for 60 seconds per position (eyes open & closed). Subjective evaluations included a subjects' VAS of mood, sedation, and driving quality, and Groningen Sleep Quality Questionnaire; also the VAS of driving instructor on the sedation of subjects.

The conclusions of the trial by Leufkens and associates were that results on all of the morning tests showed impaired performance (reaching statistical significance of $p< 0.001$ for each type of assessment, and most of the individual tests of the assessments) after middle-of-the-night administration of zolpidem 10 mg. Fig. 17 indicates the results of the SDLP (standard deviation of lateral position, i.e., road sway in cm.) during driving with the various treatments. One subject was unable to take the driving test due to dizziness and nausea, and another was stopped prematurely due to excessive drowsiness. The drug effect on driving indicated by the SDLP change indicated that zolpidem 10 mg at 5 to 6 hours post-dose produced effects of greater magnitude than an alcohol level (BAC of 0.5 mg mL^{-1}) considered the legal limit in most countries. The authors state that the standardized highway driving test and divided attention test have been found to be the most sensitive measures of sedation (Vermeeren, 2002), possibly because they are of longer duration and require continued high attention focus compared to the short psychomotor and memory tests.

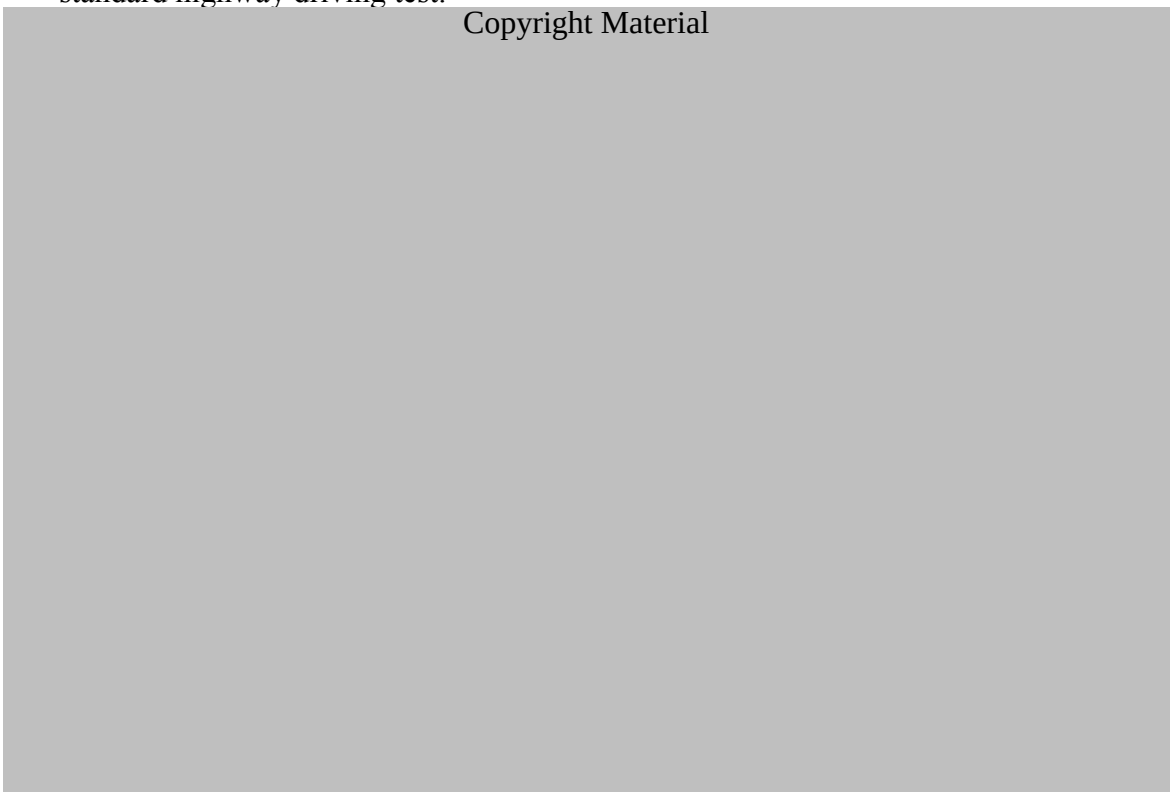
Fig. 17 Mean + S.E. of the standard deviation of lateral position (SDLP) by treatment.



Source: Leufkens T, et. al., J. Sleep Res, 2009

Although residual effects for zolpidem 10mg are usually considered resolved by 8 to 10 hours post-dose, there may be moderate-to-severe performance impairments at 5 hours post-dose that may be detectable until 7 hours post-dose (Vermeeren, 2004). Fig. 18 shows the residual effects of short half-life hypnotics on driving using a highway driving test (standard deviation of lateral position) in morning and afternoon tests. Also shown (by vertical broken lines) are mean changes produced by blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 g/L. The zolpidem 10 mg at 4 to 5 hours post middle-of-the-night dose was rated as comparable to a BAC of ~0.7 mg mL^{-1}.

Fig. 18. Residual effects of short half-life hypnotics on driving performance as measured in a standard highway driving test.



Source: Vermeeren A, 2004 (Note: 104 = Verster,2002; 82= Vermeeren A, et. al., 1998; 103= Vermeeren A, et. al., 1995)

A 2-part trial evaluated alcohol vs. placebo (Part 1), and 2 dose-strengths (10 mg & 20 mg) each of zolpidem and zaleplon vs. placebo (Part2) for driving and cognitive assessments (Verster 2002). Appendix Table 2 summarizes the results. Both zolpidem 10 mg and 20 mg showed impaired driving performance, but the author concluded that although zolpidem 10 mg showed statistically significant increase in SDLP, the magnitude of difference (+ 3.8 cm sway) from placebo was small, and speed was unaffected. The actual SDLP was 21.3 cm, and an SDLP of 18–22 cm is considered to be normal. Driving simulation and cognitive test results also showed did not show significant impairment after zolpidem 10 mg. By contrast, all driving and

cognitive measurements showed severe impairment after middle-of-the-night zolpidem 20 mg (Verster 2002).

Direct comparison isn't realistic with the data currently available, but review of previous trials using zolpidem is included here simply to try to provide a comparison to standards already available and evaluated. Comparison of sedative-hynotics to alcohol in driving impairments is problematic. There are definitely differences in the types of impairment accompanying use of alcohol compared to sleeping aids when evaluating the multiple skill sets needed for driving. Self –assessments of residual effects are not sufficiently reliable. Discussion of the comparison is mainly to address the need for more, and better designed, trials to further explore this area of safety concerns.

A review of literature on zolpidem and driving impairment was done to try to locate the plasma concentrations in cases where zolpidem was the only drug detected. A report on impaired driving in Wisconsin (Liddicoat, Harding, 2006) reported 53 cases in 2005, of which 3 cases involved no other drugs, and levels were reported as 670 ng/mL, 820 ng/mL, 4,400 ng/mL. The latter case involved zolpidem acquisition from internet sources. An article on arrests for impaired driving (Logan BK, Couper FJ., 2001) cited five separate cases, where zolpidem was the only drug detected (0.08-1.40 mg/L, mean 0.65 mg/L, median 0.47 mg/L). The signs of impairment included slow and slurred speech, slow reflexes, disorientation, lack of balance and coordination, and "blacking out." The National Highway Traffic Safety Administration site notes an additional six reported cases of accidents while driving under the influence of zolpidem, blood concentrations ranged from 0.1 to 0.73 mg/L (mean 0.31 mg/L). Unfortunately, the latter two references used blood levels rather than plasma levels, so direct comparisons can't be made; data is not available for blood to plasma concentration ratio. Studies have noted that there were few drivers with low concentrations of zolpidem. The possible reasons are that it is not being detected since tests are most sensitive for alcohol impairment, but less sensitive for other substances (Gustavsen, 2009), that low levels are not causing driving impairment, or that due to the time delay in testing, the levels are no longer high enough to qualify as a likely cause of impairment.

The authors of the Leufkens trial did not provide the mean plasma concentration level of zolpidem at the time of testing. In an attempt to compare the zolpidem 3.5 mg to the findings in the trial discussed above, Clin Pharm provided information on the 6 hour post-dose of zolpidem tartrate 10 mg (Ambien) estimated at a plasma concentration of 23.8 ng/mL based on data from Study ZI-15. By comparison, the mean morning plasma concentration level, of zolpidem SL 3.5 mg at 4 hrs post-dose would be 19.1 ng/mL. Patients taking zolpidem SL 3.5 mg should just be awakening at 4 hours post-dose, and should not be driving for at least another 30 minutes, which would place the mean plasma concentration at 16 ng/mL. All that can be said is the plasma concentration level is lower than the zolpidem 10 mg level that clearly showed impaired performance in driving, cognitive and postural stability, and lower than the levels for impaired arrests or accidents reported.

C_{max} after a single dose of 3.5 mg zolpidem sublingual tablet was ~ 47 ng/mL. After 3 hours plasma concentration would be ~ 25 ng/mL (54% of C_{max}), and 4 hours ~16 ng/mL (34% of C_{max}). At 6 hrs and 33, minutes plasma concentration would be 10% of C_{max} (~5 ng/mL).
In Study ZI-05-009, a Phase 1 PK/PD trial, the PK data showed a plasma concentration of 20 ng/mL within 20 minutes, and the PD data (change in DSST, CRT, BSR and VAS scores) were statistically significant at that plasma level. The plasma concentrations drop below that level between hour 3 and hour 4 post-dose, so driving should not be done within 4 hours after dosing, but since the PD tests used are not sensitive, it is not possible to make a more reliable recommendation on restriction of activities. The Phase 2 PD trials also suggest that there may be some accommodation occurring such that the patient is not as sensitive to a plasma concentration of ~ 20 ng/mL at 3 to 4 hours as they were at 20 minutes post-dose. However, there should be strong warnings included in labeling that driving a car, and similar activities requiring coordination and sustained attention, should not be undertaken until at least 4 hours post-dose, and longer if drug effects seem to persist. Since the zolpidem SL 1.75 mg dose showed efficacy, patients could be encouraged to use the lower dose instead if they have early morning activities that require driving-type activities. The Phase 1 and Phase 2 trials did not evaluate dosages between the 1.75 mg and 3.5 mg, but the 3.5 mg dose may have early morning plasma levels for some patients that are borderline for safety in activities.

It cannot be assumed that the margin of difference is sufficient to presume the lower dose would not also be over the safety margins for the tests, even for the average patient, much less the high-end outliers. The early morning self-assessments of alertness and performance skills by subjects do not add much clarity since subjects may not be reliable due to residual effects of which they remain unaware. These findings stress the need for additional safety testing of all the sedative hypnotics used for insomnia. Stating that the risk is probably somewhat less than the currently marketed reference drug does not adequately determine possible levels or duration of impairment. Without such testing an assessment of the risk:benefit ratio cannot be made for zolpidem SL 3.5 mg, or any of the other medications in this drug class.

Possible Effects of Dosing too Near Awakening, or Multi-dosing

The trials during the drug development phases do not completely reassure regarding residual effects. The concern remains that residual effects may be present, and increase safety risk if dosing occurs too late in the night (< 4 hours remaining bedtime), or if the recommended dosing is exceeded by taking another dose during a subsequent MOTN awakening. The pivotal trials were not able to address these concerns. Only Study ZI-06-010 used any pharmacodynamic testing (the DSST), and only at 4.5 hours post-dose. The Phase 1 PK/PD trials discussed in Section 4.4.2 provide some additional PD testing data to address the concerns, but these were all daytime trials conducted under clinic/sleep lab supervision.

The sponsor feels that the emphasis on patient-oriented instructions on how to properly self-administer the drug, in labeling and the MedGuide, as proposed in the REMS will be enough to assure compliance with proper dosing. To evaluate that claim, additional information on Study ZI-12 was requested from the sponsor. Of all the trials, only Study ZI-12 resembles the way the

drug might be used at home. Problems with self-administering the drug should be reflected in the drug accountability check. The dosing compliance from Study ZI-12 was analyzed to see how the instructions were followed at home during a clinical trial. The trial design created a maximum control situation for dosing compliance. Before the trial started, the subjects had 2 weeks of daily training in the procedure. After a middle-of-the-night awakening, subjects had to call a message center, verify that they had been awake for ≥ 10 minutes and still had at least 4 hours of bedtime remaining, before they were given permission to take the medication (or were refused because the parameters had not been met). So, generalizations made from such ideal circumstances are not a guarantee of reproducibility in the home use of the drug.

Subjects were given a 2-week supply of study medications at Visits 2 and 3. Tablet counts were done when unused medications were returned on Visits 3 and 4. During either 2-week portion of the double-blind period, a study drug deviation was counted when the number of tablets returned differed by four (4) or more from the expected number based on the IVRS record of number of tablets used. A sizable number of the subjects, 23/150 (15.3%) of the zolpidem group, and 16/145 (11.0%) of the placebo group met the criteria for protocol deviations at Visits 3 and 4 based on drug accountability (4 or more unaccounted for tablets). That yields a drug accountability issue of 13.2% for the trial. There were no incidents recorded of multi-dosing, and very few reports of inappropriate timing of dosing, but there were evident gaps in the data collection.

Late dosing: Subjects in each group reported use of the study drug on average 5 of the 7 nights per week, while the median number of MOTN calls to the IVRS was only 4 per week (Table 36). So at the request of the Agency, the sponsor conducted an analysis of the IVRS reports to determine how many calls were made when subjects had less than 4 hours of remaining bedtime. Analysis showed that 44% of the subjects in the zolpidem group, and 47% in the placebo group phoned in on at least one night for permission to use the drug when they did not have 4 hours of bedtime remaining in the night. This represents ~ 8% of the possible call-in nights for each group. Seven subjects, 5 on zolpidem (3.3%), and 2 on placebo (1.4%) called the IVRS too late for permission to dose, but took the study drug anyway. So, at least 7/295 (2.4%) of the trial subjects chose to disregard dosing instructions. Review of AEs for these subjects reported the next day indicates that one of the subjects assigned to placebo had complains of nasopharyngitis. None of the subjects had next-morning complaints of sleepiness. Ten subjects assigned to the zolpidem group did not call the IVRS, but reported that they had taken the drug at some time during the night. Only one had a next-day complaint (dry mouth).

Table 36: MOTN Calls with Less Than 4 Hours Remaining in Bed

	Zolpidem SL 3.5 mg (N=150)	**Placebo (N=144)**
Number (%) of Subjects with at least one MOTN calls with <4 hours bedtime remaining[1]	66 (44.0%)	68 (47.2%)
Total number (%) of nights when MOTN call was made with less than 4 hours [2]	335 (8.0%)	342 (8.5%)
Average number of MOTN calls per subject per week	5.08	5.03
Median number of nights of MOTN calls per week	4	4

[1] Percentages are based on the total number of subjects in the group.
[2] Percentages are based on the total number of possible nights for MOTN calls in the group (4200 zolpidem 3.5mg, 4032 placebo).

Table 37 presents **t**he distribution of nights on which the late calls were made to the IVRS. The information does not lend itself well to generalizations since there may be an under-representation. Subjects may not have been motivated to call in at times when they knew they would not be given permission to dose.

Table 37: Distribution of Number of Nights by Subject on which MOTN Calls were Made with Less than 4 hours Remaining in Bed

Number of Nights with Less Than 4 Hours Remaining in Bed	3.5 mg Zolpidem (N=150)	Placebo (N=144)
	# of Subjects	
1	16	15
2	8	9
3	6	7
4	8	6
5	6	10
6	2	3
7	5	2
8	3	4
9	1	1
10	0	0
11	2	2
12	3	4
13	2	0
14	3	0
15	0	2
16	0	0
17	1	2
18	0	1

Source: email correspondence from Transcept

The PD/PK trials ZI-05-009 and ZI-15, although daytime trials, provide the most information on the effects of the drug between hour 1 and hour 4 post-dose. This was discussed at length in Section 4.4.2. By hour 3 testing, the DSST scores were above baseline in the former trial, and <1/4 reduction from the maximum in the latter trial. Only ZI-05-009 did testing between hours 1 and 3, but the DSST scores at hour 2 and hour 2.5 were <1/3 of their maximum decrease (which occurred at 20 minutes post-dose). Overall, the PD testing seems to indicate that the onset of the drug is rapid, and sedative effects have significantly decreased by 2 to 3 hours post-dose.

Possible accidental multi-dosing: The sponsor referenced articles on retrograde amnesia contending that the probability of it occurring is limited to awakenings of < 5 minutes duration (Guilleminault and Dement, 1977, Wyatt et al., 1994). The sponsor posed a similar argument for the confusion associated with sleep inertia during middle-of-the-night awakening suggesting that it is very short-lived (Achermann et al., 1995). If used as directed (patient must be awake for 10 minutes before taking the drug), the likelihood of retrograde amnesia or sleep inertia is probably low. The drug is formulated for dissolution within 2 minutes, and the PK trials suggest a rapid absorption. The PD monitoring was first done at a 10 minute interval, but already was showing effects (although not reaching statistical significance until 20 minutes), so theoretically it is

possible that for patients falling asleep again in less than 5 minutes after taking the drug, a retrograde amnesia could occur affecting recall of the drug use, or confusion may not have cleared. In that case, a subject might re-dose on a subsequent awakening. Also, a subject might choose to re-dose since the dosage is lower than currently marketed drugs taken at bedtime for insomnia.

During the clinical review, we consulted the clinical pharmacology reviewer, Dr. Parepally, regarding the potential effects of dosing too late, multi-dosing, or using a zolpidem SL 3.5 mg for MOTN after taking an Ambien® 10 mg at bedtime. Individual plasma concentrations were obtained from Study ZI-15 to calculate primary PK parameters for 10 mg Ambien® and zolpidem SL 3.5 mg tablet. These parameters were used simulate plasma concentrations at different time points.

Fig. 19 represents the PK values if a patient used Ambien® 10 mg at bedtime, and used zolpidem SL 3.5 mg 4 hours later. The plasma levels would drop to ~ 40 ng/mL by 3 hours after the second dose, and below 25 ng/mL by 4 hours after the second dose.

Fig. 19: Predicted zolpidem plasma concentration time profile (Ambien® 10 + zolpidem 3.5 mg)

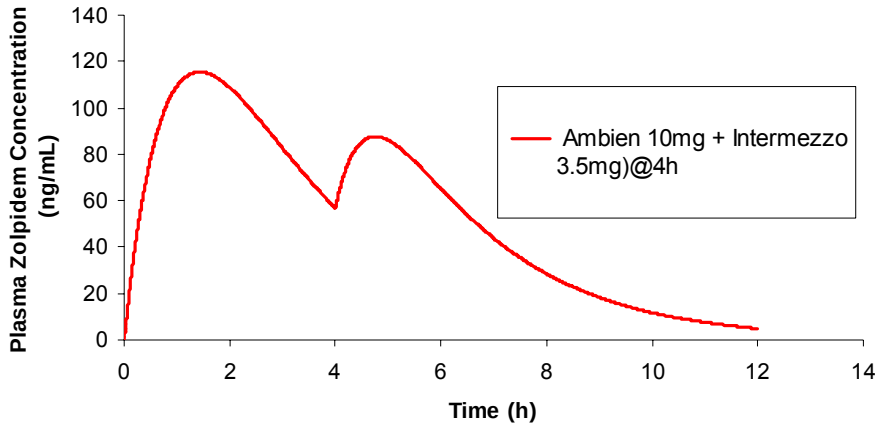
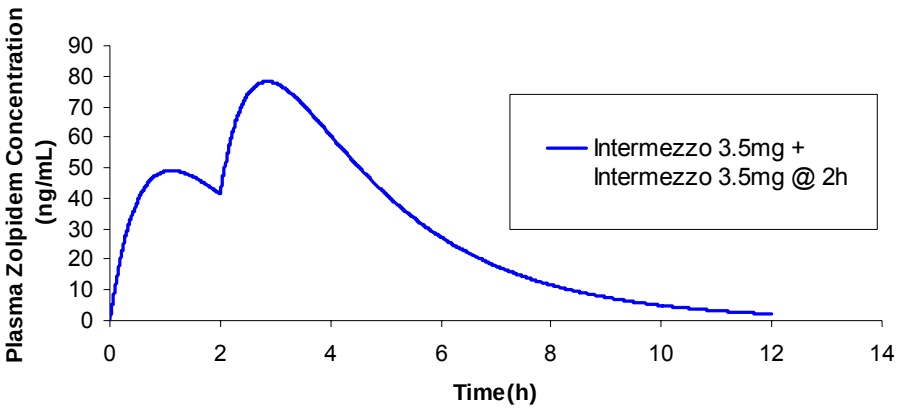


Fig. 20 represents the PK values if a patient used zolpidem SL 3.5 mg during the night (0 on the graph), and repeated the dosing 2 hours later (hour 2 on the graph). Predicted zolpidem mean concentrations at 2, 4 and 6 hours after a second dose of zolpidem SL 3.5 mg would be 60.4 ng/mL (2 hours after the second dose), 27.3 ng/mL (4 hours after the second dose) and 11.6 ng/mL (6 hours after the second dose). So, driving or other activities could not be considered safe until more than 4 hours had passed since the second dose.

Fig. 20: Predicted zolpidem plasma concentration time profile (zolpidem SL 3.5 mg + repeat)



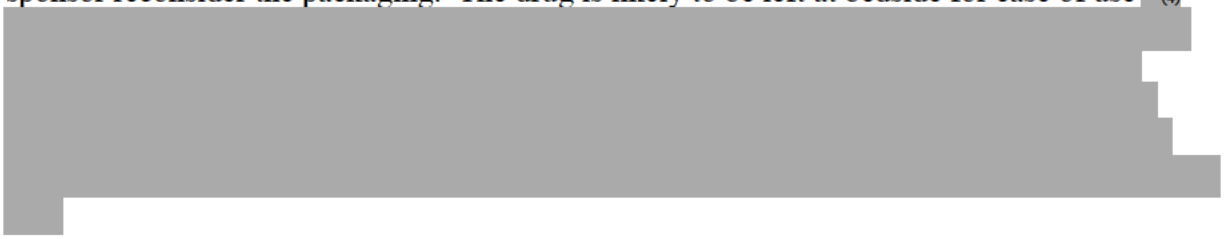
Conclusions:
Although there is the potential that the drug may not be used according to the recommendations, the PK/PD data are rather reassuring, as is the fact that the dose is much lower than that of sedatives such as Ambien® 10 mg and 5 mg currently on the market. Middle-of-the-night dosing has unique potential for errors, but the zolpidem SL 3.5 mg and 1.75 mg are not more likely to cause medication errors than the late-night (rather than HS) use of currently marketed insomnia medications for self-treatment of MOTN insomnia, which is undoubtedly occurring at present. The trial designs lacked the ideal assessments to establish the risk:benefit ratio for improper dosing occurrences, but overall, with the suggestive PD and safety data available, I would recommend the drug for approval.

Transcept's proposed plan to address dosing compliance:
The dosing compliance monitoring plan proposed by Trancept consists of the following elements (Sequence 0014, submitted May 29, 2009):

- The Medication Guide has been revised to include more prominent language concerning potential middle-of-the-night dosing concerns, (b) (4)
- (b) (4)
- A REMS plan will be submitted to track the effectiveness of the Medication Guide in communicating the risks of middle-of-the-night dosing to patients.
- Routine pharmacovigilance measures will include enhanced reporting for spontaneous adverse events (AEs) attributed to medication errors.

- Since the data from the Phase 3 trial are from a controlled environment and may not be generalizable to the "uncontrolled" use that occurs during routine clinical use, Transcept commits to develop, in collaboration with the Agency, a Phase 4, health system database study/survey to evaluate any potential AEs associated with middle-of-the-night use of zolpidem tartrate sublingual tablet.

The proposal is still under discussion with the sponsor. A review recommendation is that the sponsor reconsider the packaging. The drug is likely to be left at bedside for ease of use (b) (4)



8 Postmarket Experience

Zolpidem tartrate sublingual 3.5 mg and 1.75 mg dose strengths have not previously been approved for marketing in any country.

9 APPENDICES

9.1 Literature Review/References

9.2 Labeling

9.3 Advisory Committee Meeting

TABLES

Appendix Table 1: Table of All Clinical Trials
Appendix Table 2: Mean ± SD of performance parameters
Appendix Table 3: Description of Pharmacodynamic (PD) Measurements

Appendix Table 1. All Clinical Studies

Type of Study	**Study Identifier**	**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	Determine PK profiles of powdered zolpidem 10 mg lozenge single doses, using different swallowing times	3-way,fixed sequence, single dose, pilot study	Powdered zolpidem tartrate sublingual lozenge, 10 mg sublingual	8	Healthy Subjects	Single dose	Complete; full
BA	ZI-04-002-002	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

Table 1. All Clinical Studies, (cont.)

Type of Study	Study Identifier	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-04-003-003	Compare PK of a zolpidem formulation vs. Ambien® and determine effect of saliva swallowing regimens on PK of zolpidem formulations (5-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
BA	ZI-04-007-007	Evaluate safety, tolerability, PK, and bioavailability of zolpidem tartrate sublingual lozenge vs. Ambien®, 10 mg tablet	3-way, fixed sequence, crossover	Zolpidem tartrate sublingual lozenge,a 10 mg; sublingual Ambien®, 10 mg tablet; oral	9	Healthy Subjects	Single dose	Complete; full

Table 1. All Clinical Studies, (cont.)

Type of Study	**Study Identifier**	**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**
BE	ZI-13	Formulation bridging PK study	Randomized, open-label, two-period crossover	Zolpidem tartrate sublingual lozenge, 3.5 mg (IND formulation); sublingual Zolpidem tartrate sublingual lozenge, 3.5 mg (proposed commercial formulation); sublingual	36	Healthy Subjects	Single doses	Complete; full
PK	ZI-14	PK, safety and tolerability of 2 doses of zolpidem tartrate sublingual lozenges in elderly vs. non-elderly	Randomized, open-label, 2-way crossover for elderly (no crossover for non-elderly)	Zolpidem tartrate sublingual lozenge, 1.75 mg (elderly); sublingual Zolpidem tartrate sublingual lozenge, 3.5 mg (elderly); sublingual Zolpidem tartrate sublingual lozenge, 3.5 mg (non-elderly); sublingual	24 elderly, 24 non-elderly	Healthy elderly and non-elderly adult subjects	Single dose	Complete; full

Table 1. All Clinical Studies, (cont.)

Type of Study	Study Identifier	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	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	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

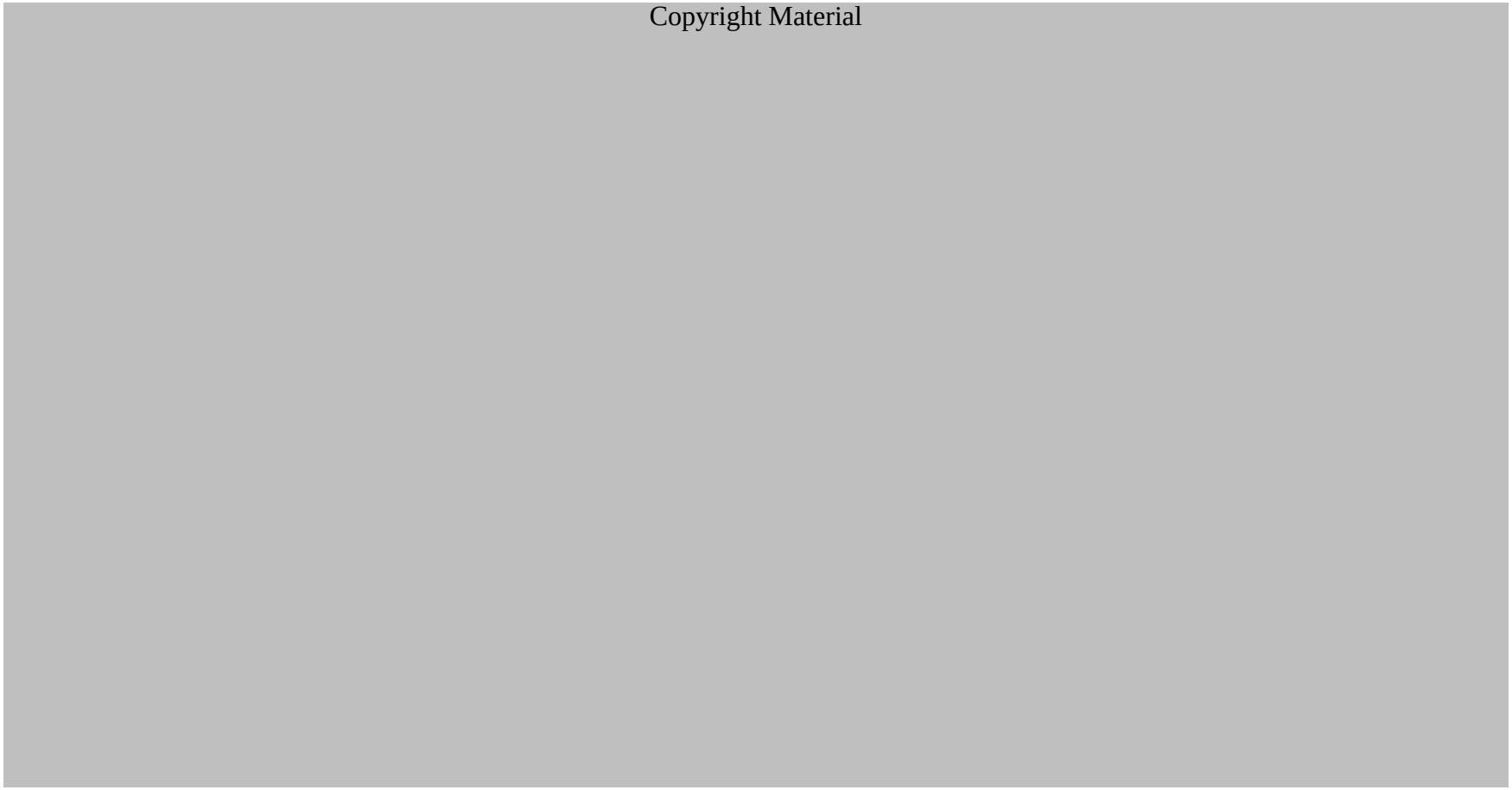
Table 1. All Clinical Studies, (cont.)

Type of Study	Study Identifier	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	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	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

Table 1. All Clinical Studies, (cont.)

Type of Study	Study Identifier	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	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	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



Source: Verster: J Clin Psychopharmacol, Volume 22(6).December 2002.576-583

Appendix Table 3: Description of the Digit Symbol Substitution Test, Symbol Copying Test, Visual Analog Scale and Buschke Memory Recall Test (simplified)

The Digit Symbol Substitution Test (DSST) is one of the tests of the Wechsler Adult Intelligence Scale (Matarazzo, 1972). It is one of many behavioral measures that vary with differing states of alertness and/or sedation. It is aversely affected by sleep deprivation and night shift work in the absence of adequate daytime sleep[c]. It is also used as a measure of drug-induced sedation, like following intake of alcohol[d] or sedative-hypnotics. The DSST is interpreted to measure complex pharmacodynamic activity, short-term memory, and fine motor control. Outcome measures are number of correct substitution during a defined time period (usually 90 seconds or 3 minutes).

Patients will be given a set of symbols with corresponding single-digit numbers. The test also will contain "blank" boxes with corresponding digits. Patients will be asked to make as many symbol-for-digit substitutions as possible working from left to right without skipping any boxes within a 90-second period. The number of correct substitutions in the 90-second period will be recorded. Patients will need to be monitored while filling out the forms.

The Symbol Copying Test (SCT) is a test with identical graphomotor requirements as the DSST but without visual search, memory, or coding demands. Outcomes are considered noncoding motoric equivalent measures to the DSST. SCT is as widely used and as sensitive as the DSST including measurement of the acute and residual effects of flurazepam and triazolam. Outcome measure is number of correct symbols copied during a defined time period (usually 90 seconds or 3 minutes).

Patients will be given a sheet filled with double rows: the upper row will be filled with symbols, the lower row will be empty. Patients will be asked to make as many and accurate symbol-copies as possible working from left to right without skipping any boxes within a 90-second period. The number of correct copies in the 90-second period will be recorded. Patients will be monitored while filling out the forms.

Visual Analog Scale (VAS): Patients will be asked to score the following question: "How alert do you feel right now?" On a 100 mm VAS, a score of 0 indicates "very sleepy" and a score of 100 indicates "wide awake and alert". The length of the VAS response will be recorded.

Buschke Word Recall Test is applied with many (minor) variations. Usually, a list of 10–15 words is presented at a constant rate for one or more trials over a given period of time; the number of words recalled is tested after each trial. A variation includes selective reminding only of items forgotten on a given trial. Depending on the time interval for retrieval, this test is believed to measure retrieval from short-term memory, retrieval from long-term memory, and long-term memory storage. This test is one of the most widely used tests for memory impairment or drug effects on memory (O'Connell 2002). Outcome measure is the number of correct words recalled under defined circumstances. The patient is to recall as many words as possible in any order. A list of 15 words will be read, at a rate of one word per second, during each test session.

Immediately after the reading, patients will write as many words down on paper as they remember. Patients will be given 1 minute to recall as many words as possible. The scores of this test are the number of words properly recalled.

Pharmacodynamic Tests should be given in the following order: 1) DSST, 2) SCT, 3) VAS, and 4) Buschke Memory Recall Test (simplified).

9.2 Literature Review/References

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9.3 Advisory Committee Meeting

No Advisory Committee meetings are scheduled, or contemplated for this NDA.

9.4 Labeling Recommendations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22328	ORIG-1	TRANSCEPT PHARMACEUTICALS INC	ZOLPIDEM TARTRATE LOZENGE

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

/s/

CAROLE L DAVIS
09/02/2009

RONALD H FARKAS
09/03/2009