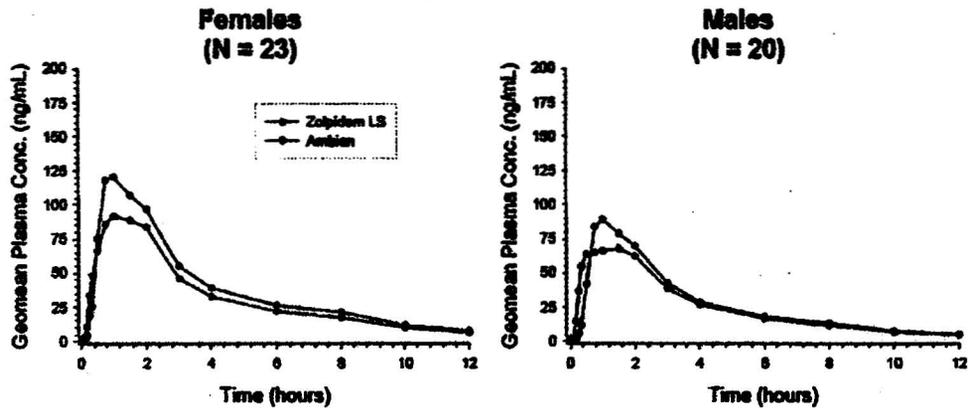


5 mg Dose



10 mg Dose

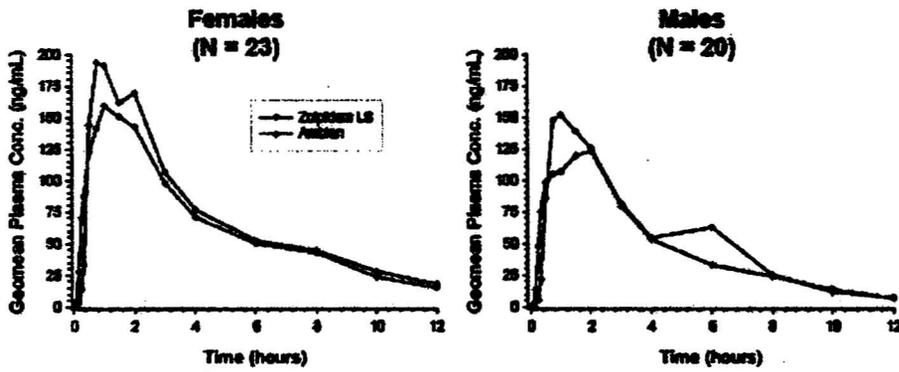


Table 10: Summary of Mean (SD) Pharmacokinetics for Males and Females by Randomized Treatment Groups

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Parameter	Zolpidem LS				Ambien Tablet				p-Values ^a		
	5 mg		10 mg		5 mg		10 mg		Gender	Gender*Trt.	Treatment
	Male (n=20)	Female (n=23)									
T _{max} (min)	51.3 (40.62)	58.3 (33.05)	54.3 (34.15)	49.6 (34.37)	58.5 (23.29)	46.3 (15.61)	63.8 (30.73)	54.1 (28.15)	0.2565	0.1638	0.3520
C _{max} (ng/mL)	197.4 (60.08)	254.9 (92.81)	188.5 (57.39)	227.8 (78.10)	206.1 (54.42)	280.0 (88.82)	186.5 (61.79)	246.7 (85.77)	< 0.0001	0.7735	0.0799
AUC _{0-t} (ng-h/mL)	678.6 (225.50)	900.3 (404.49)	644.4 (224.28)	894.4 (327.56)	708.2 (238.56)	1011.8 (332.97)	640.0 (184.19)	1001.9 (428.71)	< 0.0001	0.7476	0.2165
AUC _{0-∞} (ng-h/mL)	714.5 (251.10)	995.9 (517.14)	683.6 (255.23)	1034.3 (520.48)	753.9 (281.24)	1126.2 (480.86)	690.1 (221.89)	1167.1 (630.12)	< 0.0001	0.7016	0.2373
K _a (min ⁻¹)	0.0048 (0.00090)	0.0042 (0.00118)	0.0047 (0.00098)	0.0039 (0.00138)	0.0048 (0.00124)	0.0042 (0.00121)	0.0048 (0.00114)	0.0046 (0.00185)	< 0.0001	0.9375	0.4591
t _{1/2} (min)	148.03 (29.01)	177.1 (54.54)	156.4 (37.36)	202.2 (89.74)	155.9 (42.43)	178.9 (58.48)	154.0 (42.07)	207.6 (93.04)	< 0.0001	0.4550	0.0808
Cl/F (L/hr)	17.8 (15.22)	13.6 (10.53)	17.4 (8.81)	11.8 (5.72)	15.1 (5.82)	10.4 (4.08)	16.3 (5.56)	12.2 (11.35)	< 0.0001	0.7016	0.2373
Cl/F/kg (L/hr/kg)	0.224 (0.1841)	0.205 (0.1702)	0.218 (0.1156)	0.174 (0.0781)	0.192 (0.0874)	0.156 (0.0867)	0.208 (0.0867)	0.177 (0.1363)	0.1239	0.9724	0.3300
ln Cl/F/kg ^b	-1.6909	-1.7821	-1.6626	-1.8374	-1.7836	-1.9519	-1.6704	-1.9277	0.0002	0.7016	0.2373
Vd/F (L)	60.9 (48.84)	55.4 (44.78)	61.9 (25.88)	52.73 (25.95)	52.6 (12.53)	48.8 (9.40)	56.8 (12.49)	47.8 (15.69)	< 0.0001	0.8230	0.0939
Vd/F/kg (L/kg)	0.759 (0.5816)	0.825 (0.7083)	0.770 (0.3230)	0.762 (0.3262)	0.656 (0.1576)	0.602 (0.1469)	0.713 (0.1848)	0.692 (0.1940)	0.6738	0.8230	0.0939
Dose (mg/kg)	0.063	0.074	0.126	0.148	0.063	0.074	0.126	0.148	0.0043	ND	ND
Dose (mg/kg/m ²)	0.190	0.194	0.381	0.387	0.190	0.194	0.381	0.387	0.5243	ND	ND

ND = not done
^a = All p-values are from ANOVA based on the ln of ratios of LS-Means with the exception of T_{max}, K_a and dose expressed as mg/kg and mg/kg/m².
^b = Data are the LS-Means expressed as the ln for clearance corrected for body weight. All other means are arithmetic means.
Cross-reference: Table 14.2.2.1; Appendix 16.1.9.2.1.1; Appendix 16.1.9.2.1.4

Table 11: Analysis of Bioequivalence for Treatment Groups with Pharmacokinetic Parameters Normalized to a Dose of 10 mg

Parameter	Treatment Comparisons	LS Means		Ratio	Lower 90% CI	Upper 90% CI
		Reference	Test			
AUC 0-t						
	A vs. D	714.80	749.57	0.954	0.849	1.072
	B vs. D	804.54	749.57	1.073	0.955	1.206
AUC 0-∞						
	A vs. D	761.44	813.45	0.936	0.831	1.055
	B vs. D	862.58	813.45	1.060	0.941	1.195
C max						
	A vs. D	205.47	205.64	0.999	0.886	1.127
	B vs. D	230.91	205.64	1.123	0.995	1.267

Treatment A = 5-mg Zolpidem LS
Treatment B = 5-mg Ambien Tablet
Treatment C = 10-mg Zolpidem LS
Treatment D = 10-mg Ambien Tablet

Table 12: Primary PK parameters (NVD-ZOLP-PHI-003) - Reviewer's analysis

Parameter	Treatment Comparisons	LS Means		Ratio	Lower 90% CI	Upper 90% CI
		Reference	Test			
AUC 0-∞	A vs. D	770.39	818.77	0.953	0.845	1.047
	B vs. D	871.20	818.77	0.936	0.955	1.184
C max	A vs. D	207.59	208.01	0.998	0.894	1.136
	B vs. D	233.80	208.01	1.123	1.007	1.254

- A Zolpidem LS 5 mg
- B Ambien tablet 5 mg
- C Zolpidem LS 10 mg
- D Ambien tablet 10 mg (Reference)

Treatment B (5 mg Ambien tablet) did not meet the criteria for bioequivalence when compared to 10 mg Ambien tablet (reference) for Cmax with a ratio (90% CI) of 1.123 (0.995, 1.267). However, 90% confidence interval was within 80-125 for AUC.

Percentage of Subjects Achieving Detectable Concentration and Minimum Effective Concentration (≥20 ng/mL)

A summary of the percentage of subjects who achieved this concentration in the early postdosing period is presented in table below.

Table 13: Percentage of Subjects Achieving a Zolpidem Concentration of ≥20 ng/mL by Treatment Group in the Early Post-Dosing Period

Time (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg	Zolpidem LS 5 mg	Ambien Tablet 10 mg	Zolpidem LS 10 mg	Ambien Tablet 10 mg
5	0.0	0.0	0.0	0.0	4.7	0.0
	p = 1.0000		p = 1.0000		p = 0.5000	
10	23.3	0.0	23.3	2.3	44.2	2.3
	p = 0.002		p = 0.0117		p < 0.0001	
15	62.8	18.6	62.8	25.6	79.1	25.6
	p = 0.0005		p = 0.0009		p < 0.0001	
20	76.7	39.5	76.7	60.5	90.7	60.5
	p = 0.0009		p = 0.1435		p = 0.0010	
30	83.7	86.0	83.7	95.3	93.0	95.3
	p = 1.0000		p = 0.1797		p = 1.0000	

Results are presented as the percentage of subjects who achieved a concentration ≥20 ng/mL at each time period.
Cross-reference: Table 14.2.4.2; Appendix 16.1.9.2.1.10

A transient difference was seen when plasma concentrations of zolpidem were compared between zolpidem LS group and 10-mg Ambien tablet group. Though significant difference was observed at 10 and 15 minutes post-dosing the percentage of subjects with detectable concentrations following the 10-mg Ambien tablet (60.5%) was not significantly different (p = 0.1435) than following administration

of any of the zolpidem LS doses (76.7%). According to the sponsor, since no difference was observed at 30 minutes and later time points these differences are clinically insignificant. When the 10 mg doses were compared, a significantly greater percentage of subjects treated with zolpidem LS ($p \leq 0.0010$) achieved a zolpidem plasma concentration $>20\text{ng/mL}$ from 10 to 20 minutes following dosing, but no difference was noted at 30 minutes and the differences at 20 minutes, i.e. 90.7 vs. 60.5% (for zolpidem LS 10 mg and Ambien 10 mg respectively) appear to be clinically insignificant.

Table 14: Analysis of Time to Detectable and ≥ 20 ng/mL Concentrations

Time to (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg	Zolpidem LS 5 mg	Ambien Tablet 10 mg	Zolpidem LS 10 mg	Ambien Tablet 10 mg
First Detectable Concentration	7.0	17.4	7.0	15.3	6.5	15.3
	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
≥ 20 ng/mL Concentration	22.7	27.2	22.7	23.3	17.0	23.3
	$p < 0.0001$		$p = 0.0015$		$p < 0.0001$	
Data represent the means of the time to first detectable concentration and time to a concentration ≥ 20 ng/mL. Cross-reference: Table 14.2.5; Appendix 16.1.9.2.1.11						

The time to the first detectable concentration was significantly shorter ($p < 0.0001$) for zolpidem LS, with mean times of 7.0 and 6.5 minutes for the 5- and 10-mg doses, than for Ambien tablets, with mean times of 17.4 and 15.3 minutes for the 5- and 10-mg doses, respectively. Likewise, the time to a concentration ≥ 20 mg/mL was also significantly shorter for zolpidem LS ($p \leq 0.0010$), averaging 22.7 and 17.0 minutes for the 5- and 10-mg doses, than for Ambien tablets, averaging 27.2 and 23.3 minutes for the 5- and 10-mg doses, respectively. The clinical significance of this difference is unknown.

PD Assessments: Assessment of drowsiness/alertness was done at all treatment visits, within 15 minutes prior to dosing and at 12, 13, 22, and 23 minutes after dosing.

At Study Visits 2 to 5, within 15 minutes prior to dosing and at 12 and 22 minutes after dosing, subjects self-assessed their drowsiness (ranging from “a little” to “a lot”) on a 100-mm VAS for each of the following 12 descriptors of sedation: drowsy, slowed down, sleepy, sedated, tired, worn out, listless, fatigued, exhausted, sluggish, weary, bushed. At the same visits, subjects performed the Digit Symbol Substitution Test (DSST), a measure of attention, perceptual speed, motor speed, visual scanning and memory, within 15 minutes prior to dosing and at 13 and 23 minutes after dosing.

Table 15: Analysis of the Digit Symbol Substitution Test for Change from Baseline for Full Analysis

Time (minutes)	Zolpidem LS 5 mg (N = 43)	Ambien Tablet 5 mg (N = 43)	Zolpidem LS 10 mg (N = 43)	Ambien Tablet 10 mg (N = 43)
13	-8.2 (8.39)	-3.3 (7.57)	-13.6 (13.15)	-3.7 (8.49)
23	-7.9 (9.70)	-8.6 (10.45)	-19.7 (16.02)	-15.4 (16.09)
Data are presented as the mean (SD) Cross-reference: Table 14.2.6.2; Appendix 16.1.9.2.2.1				

Table 16: Analysis of DSST Change from Baseline Scores with Confidence Intervals for Treatment Differences in Full Analysis

Time (minutes)	Zolpidem LS 5 – Ambien 5	Zolpidem LS 5 – Ambien 10	Zolpidem LS 10 – Ambien 10
13	-5.00 (-8.84, -1.16) <i>p</i> = 0.005	-4.28 (-8.15, -0.41) <i>p</i> = 0.008	-9.63 (-13.54, -5.73) <i>p</i> < 0.001
23	0.80 (-4.31, 5.90) <i>p</i> = 0.680	7.21 (2.02, 12.41) <i>p</i> = 0.011	-4.78 (-10.01, 0.45) <i>p</i> = 0.081

Data are presented as the difference between groups (95% CI). *P*-values are from the rank ANOVA
Cross-reference: Table 14.2.6.4; Appendix 16.1.9.2.2.1

At 13 minutes following dosing, there is a transient but significantly greater decrease in DSST scores for all differences between zolpidem LS and Ambien tablets ($p \leq 0.008$) although this difference for zolpidem LS disappear by 23 minutes following dosing. There is a significantly greater decrease in the arousal state at 13 minutes following dosing with zolpidem LS 5 or 10 mg compared to either Ambien 5 or 10 mg tablets but these differences are transient and lack effect at 23 minutes.

Table 17: Analysis of DSST Change from Baseline Scores with Confidence Intervals for Treatment Differences in First Treatment Period Only.

Time (minutes)	Zolpidem LS 5 – Ambien 5	Zolpidem LS 5 – Ambien 10	Zolpidem LS 10 – Ambien 10
13	-8.50 (-15.73, -1.27) <i>p</i> = 0.032	-6.82 (-13.90, 0.26) <i>p</i> = 0.050	-6.96 (-14.22, 0.313) <i>p</i> = 0.049
23	0.95 (-9.41, 11.32) <i>p</i> = 0.780	5.59 (-4.78, 15.96) <i>p</i> = 0.417	-1.15 (-11.78, 9.47) <i>p</i> = 0.999

Data are presented as the difference between groups (95% CI). *P*-values are from the rank ANOVA
Cross-reference: Table 14.2.6.8; Appendix 16.1.9.2.2.2

The results for analysis of change from baseline scores for the first treatment period only are similar to those employing all treatment periods. At 13 minutes post dosing both the zolpidem LS 5 mg and 10 mg doses produced significantly greater decreases in DSST scores indicating a decrease in the arousal state at 13 minutes post-dosing.

Visual Analog Scale

At each dosing visit, the VAS was administered twice within 15 minutes prior to dosing and at 12 and 22 minutes after dosing. The sedation scale employed 12 different descriptors of sedation, some of which were very closely related to each other. Data were analyzed as the change in VAS scores from baseline (mean of the two measurements taken prior to dosing) to 12 and 22 minutes postdose and reported as the 95% confidence intervals for the differences in scores between treatment groups. Only sporadic differences were noted in these results with no apparent pattern or consistency of when these differences were observed.

Pharmacokinetic Conclusions

- Zolpidem LS 5-mg and 10-mg doses are bioequivalent to the 10-mg Ambien tablets.
- There is a gender effect irrespective of dose normalization in which C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$, are significantly higher in females than in males with a significantly longer half-life and slower clearance also observed in female subjects. This effect is similar to the effect described in Ambien label.
- There was no gender by treatment effect found in any of the PK analyses.

Sponsor's Pharmacodynamic Conclusions

- The time to the first detectable concentration is significantly faster for zolpidem LS 5 mg and 10 mg than for either of the corresponding Ambien tablet doses but the difference was transient with no difference being noted at 20 and 30 minutes.
- Though time to zolpidem plasma concentrations ≥ 20 ng/mL believed to be associated with sedation is significantly shorter for both zolpidem LS doses than for the corresponding Ambien tablet doses, the difference was transient and no difference was noted at 23 minutes.
- A transient significantly greater decrease in DSST scores for both zolpidem LS doses compared to Ambien tablets was observed at 13 minutes but not at 23 minutes following dosing.

Safety Assessments: Safety was assessed by adverse events (AEs), physical examination findings (including oral soft tissue exam after zolpidem LS dosing and at the screening and final visits), vital signs, and laboratory test results.

Table 18: Summary of Adverse Events Occurring in 2 or More Subjects by Drug, Dose, and Gender (Safety Population).

Number of subjects	Ambien Tablet 5 mg ^a	Ambien Tablet 10 mg ^a	Zolpidem LS 5 mg ^a	Zolpidem LS 10 mg ^a	AE Subjects ^b
Total	45	46	45	47	48
With any AEs	3 (1 M; 2F)	12 (5 M; 7F)	8 (4 M; 4F)	14 (6 M; 8F)	27 (12 M; 15 F)
With treatment-related AEs ^c	2 (0M; 2F)	11 (4M; 7F)	2 (1M; 1F)	11 (4M; 7F)	20 (8M; 12F)
<p>M, male; F, female</p> <p>^a - The gender of the subject with an AE was derived from the demographic listing (Appendix 16.2.4.1) and manual counts of subjects with AEs were then performed.</p> <p>^b - Manual counts of subjects were performed from the AE listing (Appendix 16.2.7.1).</p> <p>^c - Manual counts of subjects were performed from the AE listing (Appendix 16.2.7.1) for AEs classified by the investigator as having certain, probable, or possible relationship to study drug</p> <p>Cross-reference: Table 14.3.1; Appendix 16.2.4.1, Appendix 16.2.7.1</p>					

The most common AEs were diplopia, dizziness, euphoric mood, headache, and nausea. Among the AEs only dizziness occurred in more subjects after zolpidem LS 10 mg than after Ambien 10 mg. In order of decreasing incidence, dizziness, diplopia, and headache were the most common AEs among

females, while euphoric mood, diplopia, and dizziness were the most common AEs among males. There were no AEs indicative of local adverse reactions in the oral cavity after treatment with either dose of zolpidem LS.

No subjects experienced SAEs or died. Two subjects discontinued treatment due to vomiting possibly related to study drug, including 1 subject who received Ambien 10 mg and 1 subject who received zolpidem LS 10 mg. One subject discontinued due to an animal bite unlikely to be related to treatment with zolpidem LS 10 mg.

Comment to the Medical Officer:

The medical officer should review the above safety and pharmacodynamic assessments in greater detail.

NVD-ZOLP-PHI-004: A Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Elderly Volunteers

Study Title	A Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Elderly Volunteers
Study number	NVD-ZOLP-PHI-004
Study Period	12 January 2007 to 23 March 2007
Study Director	Evin H. Sides III, MD
Study Design	Single-Center, Randomized, 2-way Crossover, Open-Label, Multiple-Treatment Pharmacokinetic Study

Study Population: N=24,

Age: ≥ 65 years

Gender: Healthy Elderly Male or Female

BMI: ≤ 30 Kg/m²

Objectives:

- To compare the PK profile of the 5-mg dose of zolpidem LS to the 5-mg Ambien tablet (Sanofi-Aventis) in healthy elderly male and female volunteers under fasting conditions.
- By design, to evaluate any potential gender-effect by comparison of key PK parameters in males versus females.
- To provide safety and tolerability information about oral spray administration of zolpidem in healthy elderly male and female volunteers.
- To provide assessment of pharmacodynamic properties of zolpidem LS as measured by the drowsiness/alertness levels associated with study drug administration.

Treatment Groups: Treatment 1 "A" : Zolpidem LS 5 mg (fasting)
Treatment 2 "B" : Ambien tablet 5 mg (fasting)

Washout period was 7±3 days

Sampling: Blood samples (5.0 mL/sample) immediately before dosing and at 5, 10, 15, 20, 30, 45, 60, 90 minutes, and 2, 3, 4, 6, 8, 10 and 12 hours following dosing

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

This is a randomized study. Each subject received each treatment according to the randomization code.

Analytical

Assay performance during the study was acceptable, refer to table 18.

Table 19: Assay Performance During Study NVD-ZOLP-PHI-004

Parameter	Quality Control Samples	Standard Curve Samples
Quality Control or Standard Curve Concentration (ng/mL)	3, 60, 190	1, 2, 4, 10, 50, 100, 200, 300
Between Batch Precision (% CV)	6.6 to 7.7	2.0 to 6.2
Between Batch Accuracy (% nominal)	99.4 to 100.9	93.8 to 108.6
Linearity	Weighted linear equation ($1/x^2$), $r = 0.9970$	
Linear Range (ng/mL)	1 to 300	
Sensitivity/Lower Limit of Quantification (ng/mL)	1	

Selection of Doses in the Study

The 5-mg dose of zolpidem LS used in the study was chosen to correspond to the 5-mg dose of Ambien tablet. Elderly subjects have been shown to have increased C_{max} and AUC and lower clearance of zolpidem when compared to younger subjects, and current recommendations indicate a lower clinical dose of zolpidem (5 mg) in this population.

Pharmacokinetic Measurements:

Pharmacokinetic Parameters Assessed

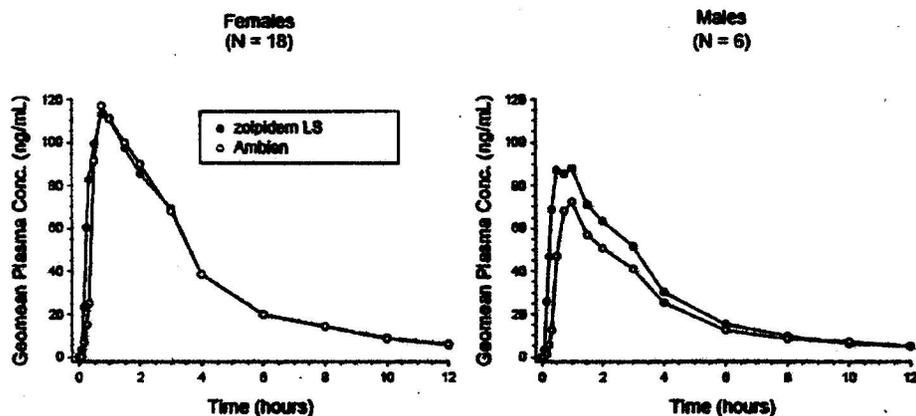
The AUC to the last measurable observation (AUC_{0-T}) and extrapolated to infinity ($AUC_{0-\infty}$), C_{max} , T_{max} , T_{obs} , $T_{1/2}$, and other appropriate pharmacokinetic parameters (i.e., clearance [Cl/F] and volume of distribution [V_d/F]) were summarized.

Detectable Drug Concentration and Drug Concentration Associated With Sedation

The percentages of subjects reaching a drug concentration ≥ 20 ng/mL by 5, 10, 15 (primary), 20, and 30 minutes postdosing, and the percentages of subjects with a detectable drug concentration by 5, 10, and 15 minutes postdosing, are reported by treatment group. Response analysis was to be performed using these data for the pair-wise comparisons of 5-mg zolpidem LS vs 5-mg Ambien tablet (A vs B).

Discordances between response and non-response for each subject receiving each of the 2 treatments were analyzed using McNemar's test. The time variables T_{max} , T_{det} and T_{ther} were analyzed for the same pair-wise comparison. Each pair-wise comparison was to be analyzed using a rank analysis of variance (ANOVA) model. The p -value associated with the difference in least squares means (LS-Means) was used to test for differences in each of the time variables.

Geometric Mean Plasma Concentrations for Male and Female Subjects Following Administration of Zolpidem LS and Ambien Tablets



Analysis of Pharmacokinetic Parameters

A summary of the mean pharmacokinetic parameters for 5 mg zolpidem LS and Ambien tablets is presented in table below.

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Parameter	Zolpidem LS 5 mg		Ambien Tablet 5 mg		p-Values ^d	
	Male (N = 6)	Female (N = 18)	Male (N = 6)	Female (N = 18)	Gender	Treatment
T _{max} (min)	42.5 (19.94)	52.2 (40.08)	52.5 (20.68)	41.7 (21.35)	0.3353	0.6414
C _{max} (ng/mL)	100.0 (8.68)	144.9 (55.40)	87.1 (22.31)	141.3 (32.70)	<0.0001	0.2907
AUC ₀₋₇ (ng•hr/mL)	349.9 (69.38)	493.3 (192.71)	285.5 (68.95)	481.9 (180.53)	<0.0001	0.0699
AUC _{0-∞} (ng•hr/mL)	373.1 (92.57)	532.8 (228.69)	306.0 (83.40)	518.1 (216.97)	<0.0001	0.0707
K _a (min ⁻¹)	0.0049 (0.00161)	0.0048 (0.00130)	0.0051 (0.00235)	0.0049 (0.00127)	0.0004	0.3261
t _{1/2} (min)	153.6 (46.34)	157.1 (49.15)	155.9 (55.45)	153.1 (42.16)	0.0355	0.8268
Cl/F (L/hr)	14.1 (3.22)	11.2 (5.17)	17.6 (5.91)	11.5 (5.87)	0.0002	0.0897
Cl/F/kg (L/hr/kg)	0.191 (0.0773)	0.172 (0.0975)	0.244 (0.1333)	0.172 (0.0858)	0.0013	0.1358
ln Cl/F/kg ^b	-1.6206	-1.8934	-1.3803	-1.8789	<0.0001	0.0649
Vd/F (L)	49.1 (5.96)	38.6 (12.71)	60.3 (10.17)	38.2 (9.48)	<0.0001	0.0735
Vd/F/kg (L/kg)	0.638 (0.0894)	0.580 (0.2320)	0.782 (0.1144)	0.567 (0.1403)	0.0035	0.1336
Dose/Body Weight (mg/kg)	0.066 (0.013)	0.075 (0.011)	0.066 (0.013)	0.075 (0.011)	0.0217	ND
Dose/BMI (mg/kg/m ²)	0.192 (0.025)	0.191 (0.022)	0.192 (0.025)	0.191 (0.022)	0.9595	ND

ND = not done
^a = All p-values are from ANOVA.
^b = Data are the LS-Means expressed as the ln for clearance corrected for body weight.
 Cross-reference: Table 14.2.2.1; Appendix 16.1.9.2.1.1; Appendix 16.1.9.2.1.4

Pharmacokinetic parameters including C_{max}, AUC₀₋₇, and AUC_{0-∞} were similar across both the treatments. Across both genders and formulations the T_{max} was similar ranging from approximately 42 minutes to approximately 52 minutes with no statistically significant effect of either gender or treatment.

Means and 90% confidence intervals between the 5 mg doses of zolpidem LS and Ambien tablets for AUC₀₋₇, AUC_{0-∞}, and C_{max} are presented in the table below. The two dosage forms are bioequivalent, the confidence interval falls between 0.8 and 1.25 for each parameter.

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Table 11.2 Summary of Principal Pharmacokinetic Parameters for All Subjects Treated with Zolpidem LS and Ambien Tablets

PK Parameter	Statistic ^a	Zolpidem LS 5 mg	Ambien Tablet 5 mg
		(N = 24)	(N = 24)
T _{max} (min)	Mean (SD)	49.8 (35.95)	44.4 (21.28)
	Min, Max	15.0, 180.0	20.00, 90.00
C _{max} (ng/mL)	Mean (SD)	133.7 (51.8)	127.8 (38.40)
	Min, Max	53.0, 268.1	52.4, 188.9
AUC _{0-T} (ng•hr/mL)	Mean (SD)	457.5 (180.34)	432.8 (180.75)
	Min, Max	186.8, 975.0	158.9, 912.6
AUC _{0-∞} (ng•hr/mL)	Mean (SD)	492.9 (213.32)	465.1 (212.39)
	Min, Max	191.8, 1112.1	158.9, 1041.7
t _{1/2} (min)	Mean (SD)	156.2 (47.48)	153.8 (44.54)
	Min, Max	90.2, 266.3	72.6, 239.5

Min = minimum, Max = maximum, SD = standard deviation
^a = Means presented are the arithmetic means.
 Cross-reference: Table 14.2.1; Appendix 16.2.6.1.1

Analysis of Bioequivalence Between Treatment Groups

Parameter	Treatment Comparisons	LS-Means ^a		Difference (Test - Reference)	Ratio	Lower 90% CI	Upper 90% CI
		Reference Ambien	Test Zolpidem LS				
AUC(0-T) (ng.hr/mL)	A vs. B	398.91	427.07	28.16	1.071	0.967	1.185
AUC(0-∞) (ng.hr/mL)	A vs. B	422.84	453.93	31.10	1.074	0.968	1.190
C _{max} (ng/mL)	A vs. B	121.44	125.42	3.978	1.033	0.922	1.157

Treatment A = 5-mg zolpidem LS
 Treatment B = 5-mg Ambien Tablet
^a = Data are reported as the LS-Means.
^b = Difference between the ln of the LS-Means for reference and test values.

Percentage of Subjects Achieving Detectable Concentration of Zolpidem and Concentration Believed to be Associated With Sedation (≥20 ng/mL)

A summary of the percentage of subjects who achieved a concentration ≥ 20 ng/mL in the early post-dosing period is presented in table below.

Time (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg
5	0.0	0.0
	$p = 1.0000$	
10	66.7	8.3
	$p = 0.0001$	
15	79.2	29.2
	$p = 0.0005$	
20	95.8	54.2
	$p = 0.0063$	
30	100.0	91.7
	$p = 0.5000$	
Results are presented as the percentage of subjects who achieved a concentration ≥ 20 ng/mL at each time period. Cross-reference: Table 14.2.4.2; Appendix 16.1.9.2.1.10		

As is shown in the table below, the time to the first detectable concentration for zolpidem LS had a mean time of 5.8 minutes compared to Ambien tablet, with a mean time of 14.6 minutes. Likewise, the time to a concentration believed to be associated with sedation (≥ 20 ng/mL) was also shorter for zolpidem LS averaging 13.1 minutes compared to Ambien tablets averaging 24.0 minutes. However, DSST results show that the differences were not significant statistically among the treatments.

Table 20: Analysis of Time to Detectable and ≥ 20 ng/mL Concentrations

Time to (minutes)	Zolpidem LS 5 mg	Ambien Tablet 5 mg
First Detectable Concentration	5.8	14.6
	$p < 0.0001$	
≥ 20 ng/mL Concentration	13.1	24.0
	$p < 0.0001$	
Data represent the means of the time to first detectable concentration and time to ≥ 20 ng/mL concentration. p -Values are from ANOVA. Cross-reference: Table 14.2.5; Appendix 16.1.9.2.1.11		

Pharmacodynamic Analyses

Pair-wise comparison (A vs B) was made on change in DSST scores from baseline (mean of 2 measurements taken prior to dosing) to 13 minutes postdosing (primary pharmacodynamic endpoint) and 23 minutes postdosing. Change from baseline VAS score (mean of 2 measurements taken prior to dosing) to 12 and 22 minutes postdosing were also summarized.

Digit Symbol Substitution Test

Evaluation of pharmacodynamic effects of 5 mg zolpidem LS versus the 5 mg Ambien tablet were performed using the DSST at 13 and 23 minutes following dose administration. This test is an evaluation of attention, perceptual speed, motor speed, visual scanning, and memory. A reduction in DSST scores is considered as an indication of hypnotic effect and a marker of sleepiness and sedation. To avoid learning process that results in higher scores when the test is used repetitively, two analyses are presented; the planned analysis using the data from both treatment periods and an analysis employing data from the first treatment period only. The results of the change from baseline in DSST scores following the two treatments and measurement periods are summarized in the table below. There was no significant difference when baseline values across treatment groups were compared.

Table 21: Analysis of Digital Substitution Test for Change in Baseline for Full Analysis

Time (minutes)	n	Zolpidem LS 5 mg	Ambien Tablet 5 mg
13	22	-5.4 (9.31)	0.5 (7.77)
23	21	-7.5 (8.44)	-5.7 (10.65)
Data are presented as the mean (SD)			
Cross-reference: Table 14.2.6.2; Appendix 16.1.9.2.2.1			

Table 22: Analysis of DSST Change from Baseline Scores with Confidence Intervals for Treatment Differences in Full Analysis

Time (minutes)	Zolpidem LS 5 mg – Ambien Tablet 5 mg
13	-4.37 (-9.94, 1.19)
	<i>p</i> = 0.033
23	-1.72 (-7.03, 3.59)
	<i>p</i> = 0.270
Data are presented as the difference between groups (95% CI). <i>p</i> -values are from the rank ANOVA	
Cross-reference: Table 14.2.6.4; Appendix 16.1.9.2.2.1	

Visual Analog Scale

At each dosing visit, the VAS was administered twice within 15 minutes prior to dosing and at 12 and 22 minutes after dosing. The sedation scale employed 12 different descriptors of sedation some of which were very closely related to each other. Data were analyzed as the change in VAS scores from baseline (mean of the two measurements taken prior to dosing) to 12 and 22 minutes postdosing and reported as the 95% confidence intervals for the differences in scores between treatment groups. Only sporadic significant differences were noted in these results with no apparent pattern or consistency of when these differences were observed.