

later times. This is confirmed by the observation that there were no statistically significant differences in T<sub>max</sub> (mean T<sub>max</sub> values provided in the table below) between any of the zolpidem doses and Ambien and with a significantly lower C<sub>max</sub> when data were normalized to a 10-mg dose. The results of this study demonstrated a linear relationship to dose for mean C<sub>max</sub> and AUC<sub>0-∞</sub> over the range of doses of zolpidem LS studied. However, as the dose of zolpidem LS was increased from 2.5 to 10 mg, the mean ratio for AUC and C<sub>max</sub> were significantly reduced to 0.78 and 0.73, respectively, with the corresponding 90% CI being lower. This study further demonstrated that in terms of bioavailability (AUCs) the 2.5-mg and 5-mg zolpidem LS were bioequivalent to the 10-mg Ambien tablet when dose normalized to 10 mg. C<sub>max</sub> levels for zolpidem LS were generally lower than Ambien 10-mg tablet. Pharmacodynamic results revealed no clinically meaningful differences between zolpidem LS and Ambien. Zolpidem LS was safe and well tolerated.

Parameter <sup>a</sup>	Ambien Tablet 10 mg (n = 10)	Zolpidem LS		
		2.5 mg (n = 10)	5 mg (n = 10)	10 mg (n = 10)
<b>Time Parameters (Minutes):</b>				
T <sub>max</sub> :				
Mean ± SD	63.0 ± 28.1	52.5 ± 22.6	46.0 ± 22.1	49.0 ± 28.7
(CV, %)	(44.6)	(43.1)	(48.0)	(58.5)
Median (Range)	53 (30-120)	45 (30-90)	45 (20-90)	45 (20-120)

**Reviewer Comments:**

Internal standard \_\_\_\_\_ used in the assay was different from the internal standard \_\_\_\_\_ used in the assay of plasma samples from pivotal BE study. Partial validation was provided in the method validation report to support the change.

**NVD-ZOLP-PHI-002: A Pilot Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Male Volunteers**

Study Title	A Pilot Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Male Volunteers
Study number	NVD-ZOLP-PHI-00
Study Period	18 July 2006 to 27 September 2006
Study Director	Evin H. Sides III, MD
Study Design	Single-Center, 5-way Crossover, Open-Label, Dose-Ranging, Multiple-Treatment Pharmacokinetic Study

**Study Population: N=14**

Age: 18-45 years  
 Gender: Healthy Male  
 BMI: ≤30 Kg/m<sup>2</sup>

**Objectives:**

- To evaluate PK parameters of 5-mg and 10-mg zolpidem LS in comparison to the orally administered 10-mg Ambien tablet in healthy male volunteers under fasting conditions.
- To evaluate PK parameters of 10-mg zolpidem LS after the standard high fat breakfast in comparison to 10-mg zolpidem LS under fasting conditions.
- To collect safety and tolerability information about administration of zolpidem LS in healthy male 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" (Visit 2): Ambien tablet 10 mg (fasting)  
Treatment 2 "B" (Visit 3): Zolpidem LS 10 mg (fasting)  
Treatment 3 "C" (Visit 4): Zolpidem LS 5 mg (fasting)  
Treatment 4 "D" (Visit 5): Ambien tablet 5 mg (fasting)  
Treatment 5 "E" (Visit 6): Zolpidem LS 10 mg (fed)

Washout period was 7±3 days

**Sampling:** Blood samples (4.0 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 was a non-randomized study. Each subject received each treatment in the same sequence.

**Selection of Doses in the Study**

The 5-mg and 10-mg doses of zolpidem LS used in the study were chosen to correspond to the 5-mg and 10-mg doses of Ambien tablet. A previous pilot PK study in 10 healthy male subjects (NVD-ZOLP-014-04-PHI-001-US) using an earlier pilot formulation indicated that there were no safety or tolerability issues with these doses of zolpidem LS, and that the mean  $C_{max}$  and AUC for the 10-mg dose did not exceed that of the 10-mg Ambien tablet.

**Pharmacokinetic Measurements:**

Primary and secondary pharmacokinetic parameters were determined from the plasma concentration time profile of the individual subjects. Also time to reach detectable ( $T_{det}$ ) and time to reach therapeutic concentration ( $\geq 20$  ng/ml,  $T_{ther}$ ) were determined to assess the differences between Ambien tablets and zolpidem LS.

There was a significant decrease in exposure to zolpidem when zolpidem LS was administered with food. Under fasting conditions exposure to zolpidem was comparable after the administration of tablet and lingual spray formulations.

The mean ratios of PK parameters normalized to a dose of 10 mg for each treatment group compared to the reference treatment, Ambien 10 mg fasted, failed to meet the bioequivalence criteria for all the treatments, i.e., all of the confidence intervals fell outside the range of 0.8 to 1.25.

Figure 5: Mean Plasma Concentration of Zolpidem Following Administration of 5-mg and 10-mg Doses of Zolpidem LS and Ambien® Tablets

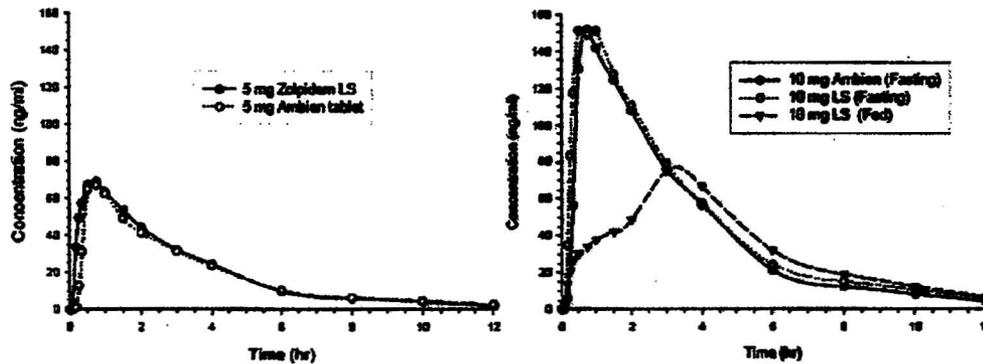


Table 5: Summary of Pharmacokinetic Parameters for Plasma Zolpidem (Per Protocol Population)

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Parameter <sup>a</sup>	Ambien Tablet 5 mg Fasted (N=9)	Ambien Tablet 10 mg Fasted (N=10)	Zolpidem LS 5 mg Fasted (N=10)	Zolpidem LS 10 mg Fasted (N=10)	Zolpidem LS 10 mg Fed (N=10)
<b>C<sub>max</sub> (ng/mL):</b>					
mean ± SD	74.6 ± 26.7	179 ± 46.8	83.8 ± 44.7	190 ± 64.7	79.7 ± 24.4
(CV)	(35.8)	(26.1)	(53.4)	(34.1)	(30.7)
median (range)	72.6 (32.2-126)	171 (108-290)	76.4 (35.2-193)	176 (120-321)	76.9 (38.0-112)
<b>AUC parameters (ng • h/mL):</b>					
<b>AUC<sub>0-7</sub></b>					
mean ± SD	226 ± 121	520 ± 189	240 ± 108	566 ± 248	402 ± 156
(CV)	(53.6)	(36.3)	(44.8)	(43.8)	(38.8)
median (range)	224 (27.9-374)	566 (116-758)	278 (87.3-390)	593 (126-1086)	435 (105-657)
<b>AUC<sub>0-∞</sub></b>					
mean ± SD	237 ± 130	535 ± 196	247 ± 114	589 ± 272	429 ± 170
(CV)	(54.9)	(36.6)	(46.2)	(46.2)	(39.6)
median (range)	228 (27.9)-384	570 (116-764)	283 (87.3-407)	615 (126-1177)	480 (105-673)
<b>Time parameters (minutes):</b>					
<b>T<sub>max</sub></b>					
mean ± SD	37.2 ± 12.28	42.0 ± 13.78	40.5 ± 22.54	45.5 ± 21.66	153 ± 60.7
(CV)	(33.0)	(32.8)	(55.7)	(47.6)	(39.7)
median (range)	30.0 (20-60)	37.5 (30-60)	37.5 (10-90)	37.5 (20-90)	180 (60-240)
<b>T<sub>1/2</sub></b>					
mean ± SD	12.2 ± 3.63	14.5 ± 6.85	6.00 ± 2.11	5.50 ± 1.58	5.00 ± 0
(CV)	(29.7)	(47.3)	(35.1)	(28.8)	(0)
median (range)	10 (10-20)	15 (5-30)	5 (5-10)	5 (5-10)	5 (5-5)
p-value <sup>b</sup>	—	—	<0.0001	—	—
p-value <sup>c</sup>	—	—	<0.0001	<0.0001	—
p-value <sup>d</sup>	—	—	—	—	0.4750

## Dose Normalized Data

Table 6: Comparison of Pharmacokinetic Parameters for Plasma Zolpidem

Parameter	Ambien Tablet 5 mg Fasted	Zolpidem LS 5 mg Fasted	Ambien Tablet 10 mg Fasted	Zolpidem LS 10 mg Fasted	Zolpidem LS 10 mg Fed
<b>C<sub>max</sub> (ng/mL)</b>					
geometric LS-Mean	139	149	174	181	76
mean ratio	0.802	0.858		1.040	0.802
90% CI <sup>a</sup> (%)	0.652, 0.988	0.697, 1.05		0.845, 1.28	(0.341, 0.516)
<b>AUC<sub>0-7</sub> (ng • h/mL)</b>					
geometric LS-Mean	345	427	468	504	365
mean ratio	0.736	0.912		1.077	0.736
90% CI <sup>a</sup> (%)	0.58, 0.94	0.715, 1.16		0.844, 1.37	0.567, 0.924
<b>AUC<sub>0-∞</sub> (ng • h/mL)</b>					
geometric LS-Mean	355	436	480	519	386
mean ratio	0.740	0.909		1.082	0.740
90% CI <sup>a</sup> (%)	0.579, 0.95	0.711, 1.16		0.847, 1.38	0.582, 0.951
<sup>a</sup> = 90% CI for the ratio of the geometric LS-Means between each treatment and Ambien 10 mg (reference) for the ln-transformed C <sub>max</sub> , AUC <sub>0-7</sub> , and AUC <sub>0-∞</sub> . Cross-reference: Table 14.2.3; Appendix 14.1.9.2.2.					

**PD Assessments:** Assessment of drowsiness/alertness was performed using Stanford sleepiness scale (SSS) and Digit Symbol Substitution Test (DSST) was used as a measure of attention, perceptual speed, motor speed, visual scanning and memory.

Significantly greater reductions in DSST scores for zolpidem LS 5 mg and 10 mg (fasted) were observed when compared with Ambien 10 mg at 13 minutes post-dosing. However, these scores were not statistically different for the 5-mg and 10 mg zolpidem LS dose at 23 minutes or later.

**Safety Assessment:** 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.

**Conclusions:**

- This study was a non-randomized, non-crossover study. Therefore, not a good BE study design and BE assessments or conclusion is only preliminary/tentative. All the treatments failed to meet the bioequivalence criteria when compared to Ambien tablet 10 mg.
- Comparable plasma concentrations were observed after the administration of zolpidem LS and Ambien tablets. Time to reach maximum concentration  $T_{max}$  was not significantly different among the different formulations.
- Administration of lingual spray with food significantly decreased  $C_{max}$  and AUC (approximately 50% decrease when compared to fasted state). The median time to reach maximum plasma concentrations ( $T_{max}$ ) ranged between 30 and 37.5 minutes for all treatments given in the fasted state and 3 hours in the fed state.

**NVD-ZOLP-PHI-003: A Definitive Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Male and Female Volunteers.**

<b>Study Title</b>	<b>A Definitive Pharmacokinetic Study of Zolpidem Lingual Spray Compared to Oral Tablet in Healthy Male and Female Volunteers</b>
<b>Study number</b>	<b>NVD-ZOLP-PHI-003</b>
<b>Study Period</b>	<b>10 January 2007 to 01 March 2007</b>
<b>Study Director</b>	<b>Evin H. Sides III, MD</b>
<b>Study Design</b>	<b>Single-Center, 4-way Crossover, Open-Label, Dose-Ranging, Multiple-Treatment Pharmacokinetic Study</b>

**Objectives:**

- To evaluate PK parameters of 5-mg and 10-mg zolpidem LS in comparison to 5-mg and 10-mg Ambien tablets in young healthy male and female volunteers under fasting conditions.
- To collect safety and tolerability information about zolpidem LS in young healthy 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.
- To evaluate gender-effect on PK parameters of zolpidem LS.

**Study Population: N=43**

Age: 18-45 years

Gender: Healthy Male (n=20) and Healthy Female (n=23)

BMI:  $\leq 30$  Kg/m<sup>2</sup>

**Treatment Groups:** Treatment A: Zolpidem LS 5 mg  
 Treatment B: Ambien tablet 5 mg  
 Treatment C: Zolpidem LS 10 mg  
 Treatment D: Ambien tablet 10 mg

Washout period was 7±3 days. All treatments were administered following a minimum of 10-hour fast.

**Dosage Administration:** Zolpidem LS was administered to each subject, without water, by spraying into the mouth, with 1 actuation of the pump for the 5-mg dose and 2 actuations of the pump for the 10-mg dose. Subjects were instructed not to swallow for a period of 30 seconds and to avoid intentional swallowing for up to 5 minutes following dosing, if possible. Ambien® tablet was administered to each subject with 240 mL of non-carbonated water. No water was given within 2 hours after either study drug administration.

**Randomization and Subject Assignment**

Subjects were randomly assigned to receive each of the 4 treatments in 1 of 4 treatment sequences, as shown in the following table:

Treatment Sequence	Treatment Visit 1 (Study Visit 2)	Treatment Visit 2 (Study Visit 3)	Treatment Visit 3 (Study Visit 4)	Treatment Visit 4 (Study Visit 5)
1: ABCD	Treatment A zolpidem LS (5 mg)	Treatment B Ambien Tablet (5 mg)	Treatment C zolpidem LS (10 mg)	Treatment D Ambien Tablet (10 mg)
2: BCDA	Treatment B Ambien Tablet (5 mg)	Treatment C zolpidem LS (10 mg)	Treatment D Ambien Tablet (10 mg)	Treatment A zolpidem LS (5 mg)
3: CDAB	Treatment C zolpidem LS (10 mg)	Treatment D Ambien Tablet (10 mg)	Treatment A zolpidem LS (5 mg)	Treatment B Ambien Tablet (5 mg)
4: DABC	Treatment D Ambien Tablet (10 mg)	Treatment A zolpidem LS (5 mg)	Treatment B Ambien Tablet (5 mg)	Treatment C zolpidem LS (10 mg)

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

**Analytical Methods**

Plasma concentrations of zolpidem were measured using high performance liquid chromatography (HPLC) method with mass spectrometric (MS/MS) detection \_\_\_\_\_ was used as an internal standard. Plasma samples were processed by protein precipitation and analyzed using reversed-phase HPLC with MS/MS detection.

b(4)

Table 7: Assay Performance During Study NVD-ZOLP-PHI-003

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)	6.2 to 7.4	2.3 to 4.7
Between Batch Accuracy (% nominal)	99.3 to 103.9	95.3 to 103.5
Linearity	Weighted linear equation ( $1/x^2$ ), mean $r = 0.9987$	
Linear Range (ng/mL)	1 to 300	
Sensitivity/Lower Limit of Quantification (ng/mL)	1	

**Pharmacokinetic Measurements:**

Pharmacokinetic parameters were calculated for each subject from the plasma concentration levels of zolpidem. The area under the concentration-time curve (AUC), maximum drug concentration ( $C_{max}$ ), time to maximum drug concentration ( $T_{max}$ ), time to first detectable drug concentration (values exceeding the limit of quantification) ( $T_{det}$ ), time to plasma drug concentration believed to be associated with sedation ( $\geq 20$  ng/mL) ( $T_{ther}$ ), elimination half-life ( $t_{1/2}$ ), and other appropriate PK metrics were evaluated in this study. Literature references indicate that plasma concentration of 20 ng/mL was associated with sedation according to the sponsor.

Plasma samples from Subjects 11, 15, 25, and 34 were reanalyzed because all four subjects had abnormally low zolpidem levels for at least one of the four treatment periods. The original values and the reassayed values for Subjects 11, 15, 25, and 34 did not differ significantly.

PK and PD analyses of data from Subjects 25 and 34 were considered as outliers and not used. Subject 25 was removed from all PK and pharmacodynamic analyses because all plasma concentration data following dosing with the 5 mg Ambien tablet were below limit of quantitation. Subject 34 was removed because of extremely low plasma concentrations following administration of 5 mg zolpidem LS.

**Demographics and Other Baseline Characteristics**

Demographic and baseline characteristics of the 43 subjects (20 male, 23 female) included in the PK and pharmacodynamic analyses are provided. Most subjects were Caucasian (n=22) or Black (n=18), with the remaining being Hispanic (n=2) and Asian (n=1). The average age of the 43 subjects was 29.3 years (ranging from 19 to 45 years), mean weight was 74.4 kg (54.9 to 94.8 kg), and mean BMI was 26.26 kg/m<sup>2</sup> (21.80 to 29.90 kg/m<sup>2</sup>).

Pharmacokinetic parameters for both genders combined are presented in the following table.

**Table 8: Summary of Principal Pharmacokinetic Parameters for All Subjects Treated with Zolpidem LS and Ambien Tablets**

PK Parameter	Statistic <sup>a</sup>	Zolpidem LS 5 mg (N = 43)	Ambien Tablet 5 mg (N = 43)	Zolpidem LS 10 mg (N = 43)	Ambien Tablet 10 mg (N = 43)
T <sub>max</sub> (min)	Mean (SD)	55.0 (36.48)	52.0 (20.27)	51.7 (33.94)	58.6 (29.43)
	Min, Max	15.0, 180.0	30.0, 120.0	5.00, 120.0	30.0, 120.0
C <sub>max</sub> (ng/mL)	Mean (SD)	114.1, (41.80)	122.8 (39.22)	209.5 (71.26)	218.7 (74.6)
	Min, Max	18.6, 196.5	53.3, 220.5	77.0, 401.3	100.6, 445.7
AUC <sub>0-T</sub> (ng•hr/mL)	Mean (SD)	398.6 (174.09)	434.8 (169.41)	778.1 (308.02)	833.6 (380.76)
	Min, Max	62.4, 929.2	168.8, 904.1	224.9, 1640.6	165.0, 1994.1
AUC <sub>0-∞</sub> (ng•hr/mL)	Mean (SD)	432.5 (217.24)	476.5 (219.21)	871.2 (450.20)	940.6 (539.13)
	Min, Max	62.4, 1209.8	168.8, 1279.4	229.4, 2763.6	165.04, 2971.6
t <sub>1/2</sub> (min)	Mean (SD)	163.6 (46.41)	168.7 (52.46)	180.9 (73.38)	182.7 (77.90)
	Min, Max	98.9, 302.1	92.8, 361.6	101.5, 504.5	66.7, 513.8
Min = minimum, Max = maximum, SD = standard deviation <sup>a</sup> = Means presented are the arithmetic means. Cross-reference: Table 14.2.1; Appendix 16.2.6.1.1					

**Reviewer Calculated: Summary Table**

**Table 9: Summary of Principal Pharmacokinetic Parameters for All Subjects**

PK Parameter	Statistics	Zolpidem LS 5 mg (N = 43)	Ambien Tablet 5 mg (N = 43)	Zolpidem LS 10 mg (N = 43)	Ambien Tablet 10 mg (N = 43)
T <sub>max</sub>	Mean (SD)	54.5 (35.7)	53.5 (22.5)	52.6 (34.5)	58.68 (29.5)
C <sub>max</sub>	Mean (SD)	110.5 (44.9)	119.2 (42.8)	205.5 (71)	217.5 (74.1)
AUC <sub>0-T</sub> (ng.hr/mL)	Mean (SD)	385.3 (182.0)	424.6 (177.6)	760.1 (305.5)	831.3 (372.6)
AUC <sub>0-∞</sub> (ng.hr/mL)	Mean (SD)	423.8 (236.8)	480.9 (232.1)	854.5 (483.6)	939.0 (553.0)
t <sub>1/2</sub>	Mean (SD)	174.8 (73.1)	174.8 (73.2)	176.2 (66.7)	178.0 (86.4)

Several observations of the PK profiles for zolpidem LS and Ambien tablet dosage forms are evident from the above Table. When comparing within and across dosage groups for the two formulations,  $T_{max}$  and  $C_{max}$  appears to be similar for the zolpidem LS and Ambien tablet doses, while mean AUC appear to be somewhat higher in the subjects treated with Ambien than those treated with zolpidem LS. Plasma  $t_{1/2}$  appears to be similar between the two formulations within dosage groups. Plasma half life and  $T_{max}$  were similar for zolpidem LS and Ambien tablet dosage forms.

At both the 5-mg and 10-mg doses for both zolpidem LS and Ambien tablets plasma concentration-time profile differs for male and female subjects. At different doses plasma concentrations in female subjects are higher than the male subjects but similar for both zolpimist LS and Ambien tablets.

$T_{max}$  was similar among dosages, formulations as well as genders with no effect exerted by gender ( $p = 0.2565$ ) or treatment ( $p = 0.3520$ ).

Statistically significant difference in PK parameters  $C_{max}$ ,  $AUC_{0-T}$ , and  $AUC_{0-\infty}$  was observed with gender ( $p < 0.0001$ ). All these parameters were higher for females than for males by 21 to 71% across treatment groups. Half-life was also consistently and statistically significantly longer ( $p < 0.0001$ ) for females than for males by 15 to 35%. Statistically significant gender effect on  $Cl/F$  with higher clearances in males than females ( $p < 0.0001$ ) by 28 to 47% observed, which is consistent with a shorter  $t_{1/2}$  in women.

Clearance when corrected for body weight, there was no statistically significant difference. There was a significant effect of gender on the  $Vd/F$  ( $p < 0.0001$ ) in which the volume of distribution was smaller in females than in males based on their smaller size and weight. When the volume of distribution was corrected for body weight ( $Vd/F/kg$ ) ( $p = 0.6738$ ), there was no difference statistically.

#### **Analysis of Pharmacokinetic Data Normalized to 10 mg**

PK parameters obtained from 5 mg formulations were normalized to 10 mg for bioequivalence calculations. The approved 10-mg Ambien tablet was considered the reference in these analyses.

**Figure 6: Geometric Mean Plasma Concentrations Following Administration of Zolpidem LS and Ambien Tablets**

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