

# Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name):	Zolpidem Tartrate
NDA:	22-196
PRODUCT (Brand Name):	Zolpimist™
DOSAGE FORM:	Lingual Spray
INDICATION:	Short-term treatment of insomnia characterized by difficulties with sleep initiation
NDA TYPE:	505 (b)(2)
SPONSOR:	Novadel Pharma Inc.
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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**NVD-ZOLP-PHI-003-BPR: EVALUATION OF THE EFFECT OF THE ROUTE OF ADMINISTRATION  
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**I. EXECUTIVE SUMMARY**

Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class for the short term treatment of insomnia characterized by difficulties with sleep initiation. Zolpimist is an oral spray formulation of zolpidem tartrate currently marketed under trade name of Ambien in the form of tablets. ZolpiMist was designed to show bioequivalence between this new dosage form of zolpidem tartrate and the marketed Ambien® tablets in terms of  $C_{max}$  and AUC.

ZolpiMist lingual spray will be marketed in metered dose glass containers. Each actuation of the metered dose system delivers a 5-mg dose of zolpidem tartrate in a 100- $\mu$ L spray. One and two actuations of ZolpiMist correspond respectively with the 5- and 10-mg Ambien® (zolpidem tartrate) tablets (Ambien), approved by FDA under NDA 019908 (Sanofi-Aventis).

The clinical pharmacology of zolpidem has been evaluated in 4 studies including 2 pilot studies and 2 definitive studies.

**A. Recommendation**

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 22-196. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view pending requested DSI inspection for the bioequivalence study and provided the sponsor accepts the OCP labeling recommendations.

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

Clinical Pharmacology briefing was held on 08/14/2008 and the attendees were Drs. Ramana Uppoor, Atiqur Rahman, Sripal Mada, Ting Ong, Stanley Au, Ying Fan and Ping Ji

**B. Phase IV Commitments**

None.

**C. Summary of Clinical Pharmacology and Biopharmaceutics Findings**

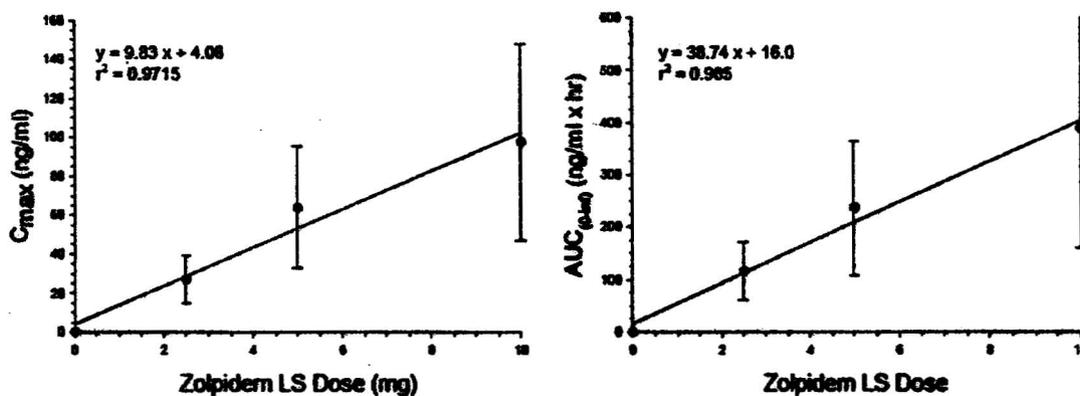
The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

**Bioequivalence:** Zolpimist™ lingual spray 5mg and 10 mg was bioequivalent to Ambien® tablets. Sponsor conducted two pivotal bioequivalence studies (Studies NVD-ZOLP-PHI-003, NVD-ZOLP-PHI-004). The 90% CI of the geometric mean ratios for the primary PK parameters ( $C_{max}$  and AUC) were contained within the prespecified intervals of 80-125%.

Secondary PK parameters of zolpidem ( $T_{max}$ ,  $t_{1/2}$ ,  $\lambda_z$ ,  $Cl/f$ , and  $V_z/f$ ) appeared to be similar between the Ambien® tablets and zolpidem lingual spray.

**Dose proportionality:** Dose-proportionality of the zolpidem plasma concentrations resulting from the administration of the lingual spray 2.5, 5 and 10 mg was also determined in one of the pilot studies (Study NVD-ZOLP-014-04-PHI-001-US). The results indicated that the lingual spray formulation was dose-proportional with respect to zolpidem PK parameters.

Figure 1: Regression analysis of  $C_{max}$  and  $AUC_{0-\infty}$  on dose of zolpidem lingual spray



Secondary PK parameters for zolpidem 5 mg and 10 mg ( $T_{max}$ ,  $t_{1/2}$ ,  $\lambda_z$ ,  $Cl/f$ , and  $V_z/f$ ) appeared to be similar between the Zolpimist and Ambien tablets.

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

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**Date**

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

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**Date**

cc: HFD-120 NDA 22196  
HFD-860 Mehul Mehta, Ramana Uppoor, Jagan Parepally

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## II. QUESTION BASED REVIEW

### A. General Attributes

#### Drug/Drug Product Information:

**Indication:** Zolpimist™ (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

#### What is the proposed mechanism (s) of action?

ZolpiMist™ (zolpidem tartrate) is an oral spray formulation of zolpidem tartrate.

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines or other drugs with known hypnotic properties. It interacts with GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. Zolpidem *in vitro* binds the (BZ<sub>1</sub>) receptor preferentially with a high affinity ratio for the  $\alpha_1/\alpha_5$  subunits. The (BZ<sub>1</sub>) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (BZ<sub>1</sub>) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (Stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

#### What is the proposed dose and dosage form?

ZolpiMist™ (zolpidem tartrate) Oral Spray (ZolpiMist), is a clear, colorless to yellowish, cherry-flavored liquid containing 5.0% w/v of zolpidem tartrate as the active ingredient. The recommended dose for adults is 10 mg once daily immediately before bedtime. The container closure is a \_\_\_\_\_ amber glass bottle and a metered-dose, snap-on, pump assembly. Each dosage unit is delivered directly into the mouth over the tongue by the pump actuation (spray). The pump is designed to deliver 5.0 mg of zolpidem tartrate per metered spray (100  $\mu$ L). The bottle for the commercial product is filled with a target amount of 8.22 g (7.7 mL) of the solution, sufficient to deliver 60 metered sprays after initial priming of the pump with 5 sprays.

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### B. General Clinical Pharmacology

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

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

**Table 1: Clinical trials in support of the Zolpimist™**

Trial ID	Study Type	Study Design	Study Duration	No. of Subjects Enrolled
NVD-ZOLP-014-04-PHI-001-US	Pilot PK study	Single-center, 4-way controlled, open-label, dose ranging, multiple-treatment, PK study	4-5 weeks	Healthy, adult (18-40 years of age) male volunteers 10
NVD-ZOLP-PHI-002	Pilot PK study	Single-center, 5-way crossover, open-label, dose ranging, multiple-treatment, PK study	5-8 weeks	Healthy, adult (18-45 years of age) male volunteers 14
NVD-ZOLP-PHI-003	Bioequivalence trial in healthy adults	Single-center, 4-way crossover, open-label, dose ranging, multiple treatment, randomized, PK study	5-7 weeks	Healthy, adult (18-45 years of age) male and female volunteers 48
NVD-ZOLP-PHI-004	Bioequivalence trial in healthy elderly subjects	Single-center, 2-way open-label, multiple-treatment, randomized, PK study	2-3 weeks	Elderly ( $\geq 65$ years) healthy male and female volunteers 24

The definitive pharmacokinetic studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004 provide bioequivalence data regarding the Zolpimist oral spray.

### C. Intrinsic Factors

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

### D. Extrinsic Factors

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

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

## E. General Biopharmaceutics

### What is the formulation of Zolpimist™ oral spray

The Zolpimist™ oral spray formulation was developed and used in definitive pharmacokinetic Studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004. The components of the oral spray are described in Table 2. The to be marketed spray is same as the one used in pivotal BE studies.

**Table 2: Components of Zolpimist™ used in clinical trials**

Component	Unit Composition (%w/v)
Zolpidem Tartrate	5.00
Artificial Cherry Flavor	
Benzoic Acid	
Citric Acid, Monohydrate	
Hydrochloric Acid	
Neotame	
Propylene Glycol	
Purified Water	

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### Is Zolpimist bioequivalent to Ambien tablets in healthy subjects?

Zolpimist lingual spray 5 and 10 mg was found to be bioequivalent to the reference Ambien tablet.

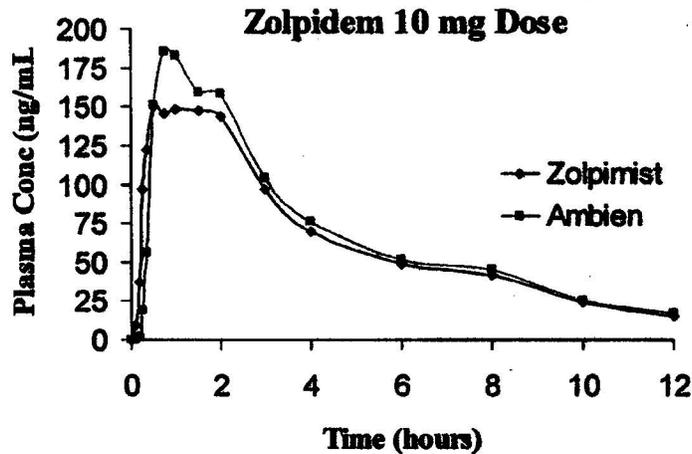
Two definitive bioequivalence studies (NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004) were conducted in healthy adults and elderly population. Bioequivalence was demonstrated based on the limits of the 90% CI of the mean treatment ratio of the PK parameters was contained within the predetermined interval of 0.8 to 1.25 as shown below.

### Study NVD-ZOLP-PHI-003 (Young Adults)

Parameter	Treatment Comparisons	Ratio	Lower 90% CI	Upper 90% CI
AUC 0-∞	B vs. C	0.953	0.846	1.074
	A vs. C	0.936	0.831	1.055
C <sub>max</sub>	B vs. C	0.947	0.839	1.069
	A vs. C	0.999	0.886	1.127

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

**Figure 2: Mean Plasma Concentration of Zolpidem Following Administration of 10 mg Doses of Zolpimist™ LS and Ambien® Tablets**



**Study NVD-ZOLP-PHI-004 (Elderly)**

Parameter	Treatment Comparisons	Ratio	Lower 90% CI	Upper 90% CI
AUC 0-∞	A vs. B	1.074	0.968	1.190
C max	A vs. B	1.033	0.922	1.157

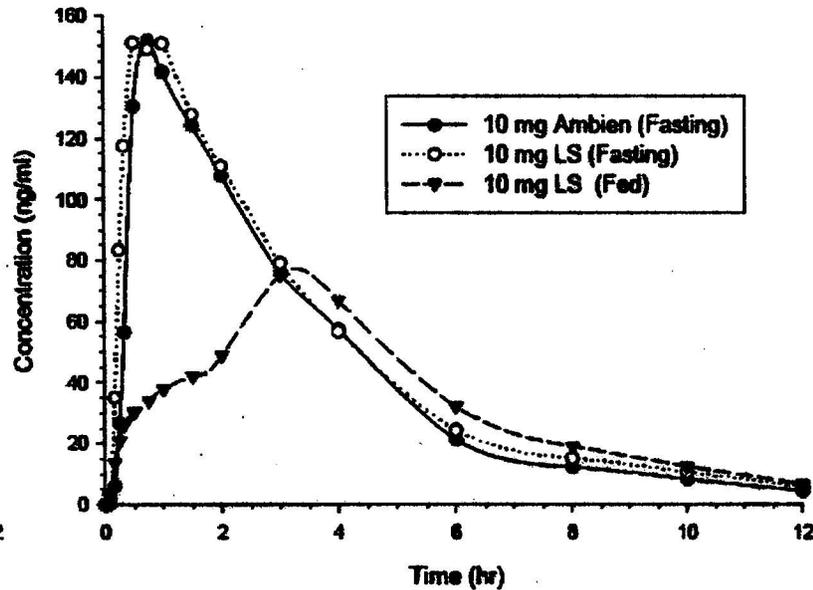
Treatment A = 5-mg Zolpidem LS  
 Treatment B = 5-mg Ambien Tablet

The mean Tmax achieved with zolpidem LS 10 mg and Ambien tablet 10 mg in study NVD-ZOLP-PHI-003 was 52.6 and 58.7 minutes. The mean Tmax achieved with zolpidem LS 5 mg and Ambien tablet 5 mg in study NVD-ZOLP-PHI-004 was 49.8 and 44.4 minutes.

**What is the effect of food on the bioavailability of Zolpimist?**

Food effect on bioavailability was studied in pilot study NVD-ZOLP-PHI-002. This study was a single-center, 5-way crossover, open-label, dose-ranging, multiple-treatment pharmacokinetic study. The administration of lingual spray with food significantly decreased C<sub>max</sub> and AUC (approximately 50% decrease when compared to fasted state). The median time to reach maximum plasma concentrations (T<sub>max</sub>) ranged between 30 and 37.5 minutes for all treatments given in the fasted state and 3 hours in the fed state. The food-effect is more prominent on zolpidem LS when compared to Ambien tablets (the mean AUC and C<sub>max</sub> from Ambien tablets were decreased by 15% and 25%, respectively, while mean T<sub>max</sub> was prolonged by 60% from 1.4 to 2.2 hr). For faster sleep onset, zolpidem should not be administered with or immediately after a meal.

**Figure 3: Mean Plasma Concentration of Zolpidem Following Administration of 10-mg Doses of Zolpidem LS and Ambien® Tablets**



**F. Analytical**

**Have the analytical methods been sufficiently validated?**

*Yes.*

*Method:* Zolpidem and the internal standard were extracted from human plasma via a protein precipitation extraction procedure. Chromatography of the reconstituted extracts was conducted using a silica analytical column and a mobile phase consisting of 50:50 methanol/ammonium formate and formic acid. Zolpidem and the internal standard were ionized in positive ion mode. MS/MS detection utilized multiple reaction monitoring.

**Pre-Study Bioanalytical Method Validation**

Information Requested	Data
Analyte	Zolpidem
Internal standard (IS)	_____

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Method description	HPLC-Reverse phase liquid chromatography with MS/MS detection
Limit of quantitation	1.0 ng/mL
Average recovery of drug (%)	71.8%
Average recovery of IS (%)	86.8%
Standard curve concentration range (ng/mL)	1-300 ng/mL
Standards Accuracy Range (%)	96.7%-104.3%
Standards precision range (%)	2.3%-5.4%
QC concentrations (ng/mL)	LQC = 3.0 ng/mL MQC = 60.0 ng/mL HQC = 190.0 ng/mL
QC precision range (%)	3.3%-5.9%
QC accuracy range (%)	101.9%-104.6%
Bench-top stability (hrs)	6 hours at room temperature.
Stock stability (days)	8 hours
Stock Solution stability (hrs) (Short Term)	44 days @ 4 °C
Wet Extract Stability	49 hours @ Ambient temperature.
In Injector stability (hrs)	68 hours @ room temperature
Freeze-thaw stability (cycles)	03 cycles.
Long-term storage stability (days)	203 days @ -70 °C
Dilution integrity	20 times of calibrator 8 (ULOQ) concentration (150 ng/mL) diluted in 50:50 ratio, CV%-2.5%, Accuracy-96.2%
Selectivity	No interfering peaks noted in blank plasma samples

Partial validation was performed to support following changes:

1. Change in internal standard from \_\_\_\_\_ to \_\_\_\_\_
2. Change in MS/MS detector to use \_\_\_\_\_
3. Change in standards range from \_\_\_\_\_ to 0.05-50 ng/mL and change in standards range from \_\_\_\_\_ to 1-300 ng/mL

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### **III. LABELING RECOMMENDATIONS**

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

**Sponsor proposed labeling text with OCP comments as track changes**

21 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

NovaDel Pharma Inc.  
Flemington, NJ 08822  
June 2008

SE-216 10 Limhamn, Sweden

Patents pending.

Prepared November 2007

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#### IV. APPENDIX

##### A Individual Study Synopsis

**Study NVD-ZOLP-014-04-PHI-001-US: A Phase I Study of Pharmacokinetics of Zolpidem Lingual Spray Compared to Oral Tablet (Pilot Study)**

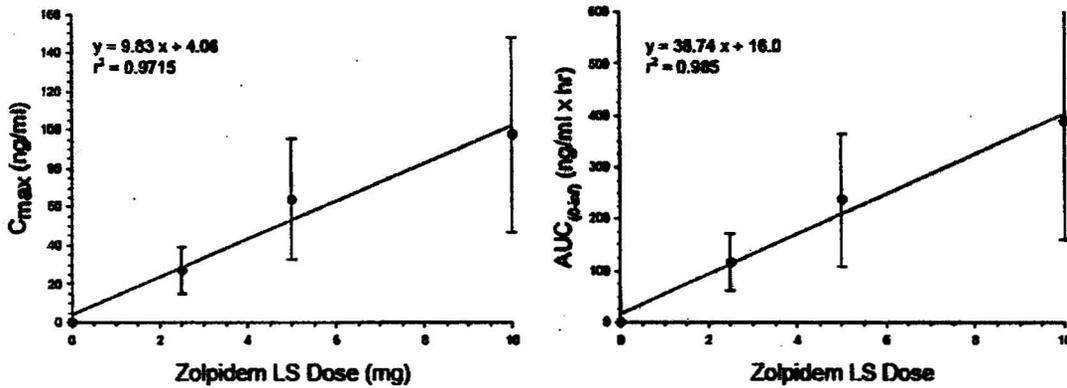
<b>Study Title</b>	<b>A Phase I Study of Pharmacokinetics of Zolpidem Lingual Spray Compared to Oral Tablet</b>
<b>Study number</b>	<b>NVD-ZOLP-014-04-PHI-001-US</b>
<b>Study Period</b>	<b>29 November 2005 to 4 January 2005</b>
<b>Study Director</b>	<b>Luis Angles, MD</b>
<b>Study Design</b>	<b>Single-center, 4-way controlled, open-label, dose-ranging, multiple-treatment, ascending-dose, PK study</b>



**Pharmacokinetic Measurements:** Pharmacokinetic parameters were calculated for each subject from the plasma-concentration levels of zolpidem.

A linear dose vs. PK relationship was seen as the dose of zolpidem LS was increased from 2.5 to 10 mg as shown in the figure below.

**Figure 4: Regression analysis of C<sub>max</sub> and AUC<sub>0-∞</sub> on dose of zolpidem lingual spray**



**Table 4: A summary of principal pharmacokinetic data**

Parameter <sup>a</sup>	Ambien Tablet	Zolpidem LS		
	10 mg (n = 10)	2.5 mg (n = 10)	5 mg (n = 10)	10 mg (n = 10)
<b>C<sub>max</sub> (ng/mL):</b>				
Mean ± SD	127.4 ± 52.0	27.0 ± 12.1	63.8 ± 31.3	97.5 ± 50.4
(CV)	(40.8)	(44.6)	(49.0)	(51.7)
Median (Range)	121 (56.5-195)	25.1 (11.7-49.3)	70.3 (18-116.7)	97.6 (37.5-174)
<b>AUC Parameters (ng<sup>h</sup>/mL):</b>				
<b>AUC<sub>0-t</sub>:</b>				
Mean ± SD	428 ± 201	107 ± 52.9	220 ± 116	366 ± 212
(CV, %)	(47.0)	(49.3)	(52.6)	(57.8)
Median (Range)	345 (140-774)	103 (35.6-193)	253 (70.1-385)	360 (91.9-662)
<b>AUC<sub>0-∞</sub>:</b>				
Mean ± SD	456 ± 213	116 ± 56.3	237 ± 128	389 ± 229
(CV, %)	(46.7)	(48.8)	(54.0)	(59.0)
Median (Range)	354 (140-821)	111 (35.6-198)	277 (72.9-418)	397 (92.0-722)

**Dose normalized data**

Parameter	Treatment Comparisons	LS-Means <sup>a</sup>		Difference <sup>b</sup> (Test - Reference)	Ratio	Lower 90% CI	Upper 90% CI
		Test	Reference				
AUC <sub>(0-T)</sub> (ng·hr/mL)	B vs A	377.3	384.4	-7.1	0.982	0.814	1.183
	C vs A	374.1	384.4	-10.2	0.973	0.807	1.174
	D vs A	301.2	384.4	-83.2	0.784	0.650	0.945
AUC <sub>(0-∞)</sub> (ng·hr/mL)	B vs A	405.3	407.8	-2.5	0.994	0.815	1.212
	C vs A	396.7	407.8	-11.0	0.973	0.798	1.186
	D vs A	315.7	407.8	-92.0	0.774	0.635	0.944
C <sub>max</sub> (ng/mL)	B vs A	98.2	116.9	-18.7	0.840	0.628	1.124
	C vs A	111.3	116.9	-5.6	0.952	0.712	1.274
	D vs A	84.9	116.9	-32.0	0.727	0.543	0.972
Treatment A = 10-mg Ambien tablet Treatment B = 2.5-mg zolpidem LS Treatment C = 5-mg zolpidem LS Treatment D = 10-mg zolpidem LS a = Data are reported as the LS-Means. b = Difference between the natural log (ln) of the LS-Means for reference and test values. Cross-reference: Table 11.2							

Overall, the mean ratios and 90% CI for AUC<sub>0-T</sub> and AUC<sub>0-∞</sub> demonstrated equivalence for the 2.5- and 5-mg zolpidem LS doses but not for the 10-mg zolpidem LS dose (where the ratio was about 0.78 that of the 10 mg Ambien tablet). The C<sub>max</sub> ratios (0.84, 0.95, and 0.73) indicated lower overall exposure to zolpidem after 10-mg zolpidem LS than Ambien tablet, with all of the 90% CI falling outside of 0.80-1.25 range; while t<sub>1/2</sub> was similar.

**Pharmacodynamic Assessments:** Self-assessment of drowsiness/sedation relative to pre dosing using a scale of 1 (much more sleepy/drowsy) to 5 (much more alert) at 15, 30, and 60 minutes after study drug administration.

**Safety Assessment:** Changes in physical examinations and safety laboratory parameters, discontinuations from the study, and adverse events (AEs).

**Safety Results:** According to the sponsor, there were no clinically significant changes in any safety laboratory parameters, vital signs, and physical examination. No AEs were reported after the administration of zolpidem LS and no subjects discontinued from the study due to safety, tolerability, or any other reason.

**Conclusions:**

The results of this study using dose-normalized data indicate that similar plasma concentrations of zolpidem are achieved after administration of zolpidem LS when compared to Ambien 10-mg tablet, while total exposure to zolpidem does not exceed that observed with Ambien tablet. Higher plasma concentrations are transiently achieved earlier with zolpidem LS than with Ambien tablet but not at