**Safety Analyses**

Subject incidence of physical examination abnormalities, oral soft tissue exam abnormalities, and laboratory abnormalities at the screening and at the final visit are summarized using frequency distribution. Subject incidence of oral soft tissue exam abnormalities were also to be summarized for the oral spray dosing visits.

Subject incidence of AEs was summarized by treatment group by severity and relatedness to the study drug. Changes in systolic and diastolic BP from baseline (predosing measurement) to postdosing evaluations (20-30 minutes, 45-60 minutes, and 2, 6, and 12 hours postdosing) are summarized for each dosing visit.

Note: Medical officer would review this section in detail.

**Pharmacokinetic and Pharmacodynamic Conclusions**

**Pharmacokinetic Conclusions**

- The two formulations, zolpimist and Ambien were bioequivalent
- Clearance was significantly slower in females consistent with significantly higher values for Cmax and AUC in females compared to males. There were no differences in pharmacokinetic (AUC, $C_{max}$ and $T_{max}$) parameters across different formulations.

**Pharmacodynamic Conclusions**

The $T_{det}$ and $T_{ther}$ were significantly shorter for zolpidem LS than for the Ambien tablet. However, differences in DSST scores were transient and not statistically significantly different at 23 minutes postdosing for both the treatments.

**NVD-ZOLP-PHI-003-BPR: Evaluation of the Effect of the Route of Administration on the Human Metabolite Pattern of Zolpidem: ZolpiMist Oral Spray Compared to Ambien Tablets**

| | |
|---|---|
| Study Title | Evaluation of the Effect of the Route of Administration on the Human Metabolite Pattern of Zolpidem: ZolpiMist Oral Spray Compared to Ambien Tablets |
| Study number | NVD-ZOLP-PHI-003-BPR |
| Study Period | June 2007 |
| Study Director | Enrique Dilone, Ph.D |

**Objective:** The purpose of this study was to determine if there were any new metabolites formed after mucosal absorption due to changes in route of administration that are not encountered via gastrointestinal (GI) absorption after tablet administration.

**Methods:**

The sponsor analyzed zolpidem metabolites from plasma taken from a randomly selected subset of 12 subjects from Study NVD-ZOLP-PHI-003, who received 5-mg and 10-mg zolpidem LS and 5-mg and 10-mg Ambien. Ratios were calculated for the area under the concentration-time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$) of each metabolite (I, II, III, IV) for each zolpidem LS dose compared to the $AUC_{0-\infty}$ of the metabolite for the corresponding tablet dose to determine any changes in the metabolism of zolpidem had occurred due to LS administration,

**Analysis of Blood Samples from Study NVD-ZOLP-PHI-003**

The concentrations of zolpidem and its four principal metabolites were determined in human plasma (potassium EDTA as the anticoagulant) samples from Study NVD-ZOLP-PHI-003 using LC/MS/MS. Samples from Subjects 4, 5, 6, 9, 11, 12, 22, 23, 37, 40, 44, and 48 for Periods I-IV were assayed.

**Metabolite LC/MS Screening and LC/MS/MS Analysis of Blood Samples from Study NVD-ZOLP-PHI-003**

A method using LC/MS/MS for the screening of zolpidem and its potential metabolites in human plasma was developed. The metabolites 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 methanol/water and formic acid. Multi ion scan MS/MS was performed on the plasma samples to screen for the potential metabolites.

**Table 23: Assay Performance in the Study**

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| Table 6.5 Assay Performance in This Study | | |
|---|---|---|
| **Parameter** | **Quality Control Samples** | **Standard Curve Samples** |
| **Analytes: Zolpidem and Metabolite I** | | |
| QC or Std Curve Conc. (ng/mL) | 3, 60, 190 | 1, 2, 4, 10, 50, 100, 200, 300 |
| Between Batch Precision (%CV)<br>• Zolpidem<br>• Metabolite I | <br>5.9–7.3%<br>4.7–5.4% | <br>0.8–6.1%<br>1.1–6.0% |
| Between Batch Accuracy (% nominal)<br>• Zolpidem<br>• Metabolite I | <br>93.1–95.3%<br>107.9–112.4% | <br>95.7–102.7%<br>93.6–107.6% |
| Linearity<br>• Zolpidem<br>• Metabolite I | Weighted linear equation ($1/x^2$)<br>Mean r = 0.9989<br>Mean r = 0.9976 | |
| Linear Range (ng/mL) | 1 to 300 | |
| Sensitivity/LLOQ (ng/mL) | 1 | |
| **Analytes: Metabolites II, III and IV** | | |
| QC or Std Curve Conc. (ng/mL) | 0.6, 12, 38 | 0.2, 0.4, 0.8, 2,10, 20,40,60 |
| Between Batch Precision (%CV)<br>• Metabolite II<br>• Metabolite III<br>• Metabolite IV | <br>4.3–6.6%<br>5.3–8.1%<br>6.0–6.8% | <br>2.3–6.0%<br>2.9–5.7%<br>1.2–5.1% |
| Between Batch Accuracy (% nominal)<br>• Metabolite II<br>• Metabolite III<br>• Metabolite IV | <br>106.3–110.9%<br>95.3–100.1%<br>93.0–97.6% | <br>93.2–106.9%<br>93.5–108.2%<br>92.9–106.5% |
| Linearity<br>• Metabolite II<br>• Metabolite III<br>• Metabolite IV | Weighted linear equation ($1/x^2$)<br>Mean r = 0.9974<br>Mean r = 0.9969<br>Mean r = 0.9974 | |
| Linear Range (ng/mL) | 0.2 to 60 | |
| Sensitivity/LLOQ (ng/mL) | 0.2 | |
| Cross-reference: Report TR-032 | | |

**Results:**

Zolpidem is converted to alcohol derivatives (metabolite III and metabolite IV)and further to carboxylic acids (metabolite I and metabolite II), which represent the main pathway of metabolism in humans. There is no renal metabolism of zolpidem. In vitro drug metabolism studies using human liver microsomes indicate the biotransformation of zolpidem by CYP isoenzymes involves mainly CYP3A4 isoforms, which appear to account for approximately 60% of zolpidem clearance. Among other isoforms, CYP2C9 is estimated to account for 22% of zolpidem clearance, CYP1A2 for 14%, and CYP2D6 and CYP2C19 together for less than 3%. Bioanalytical assay performance as shown in the table above was satisfactory.

Administration of zolpidem LS resulted in lower peak levels of all four metabolites following administration of the 10-mg dose and 5-mg dosage forms. Metabolite I accounts for the largest fraction of all four metabolites with blood levels exceeding those of the parent, zolpidem, in a number of individuals and in the mean values for the 5-mg dose. Table below summarizes the mean PK parameters for parent drug and metabolites following administration of zolpidem LS 5 mg and 10 mg

and Ambien tablets 5 mg and 10 mg. PK parameters were the AUC to the last measurable observation (AUC0–T), AUC0-∞, maximum drug concentration (Cmax), and elimination half-life (t1/2). The differences in Cmax was hypothesized to be due to the differences in the extent of "first pass metabolism" expected to be greater with the oral Ambien tablets since the entire dose would be exposed to the greater metabolic capacity of the GI route of administration. There is no evidence that the fraction of the dose absorbed in the oral cavity undergoes a greater degree of "first pass metabolism" than the fraction of the dose passing solely through the GI route since the circulating metabolite levels from the zolpidem LS doses are lower than those from the tablet doses.

**Figure 7: Plasma Profiles of Mean Plasma Concentrations of Major Metabolites of Zolpidem Following Administration of Zolpidem LS and Ambien Tablets.**

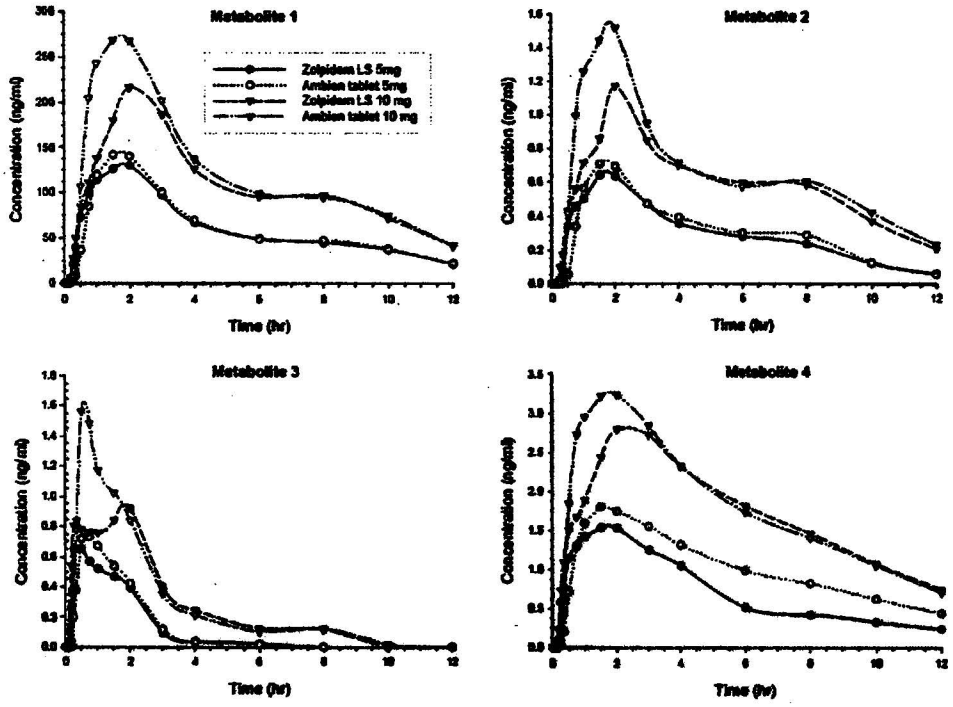


**Figure 8: Zolpidem Metabolites in Man**

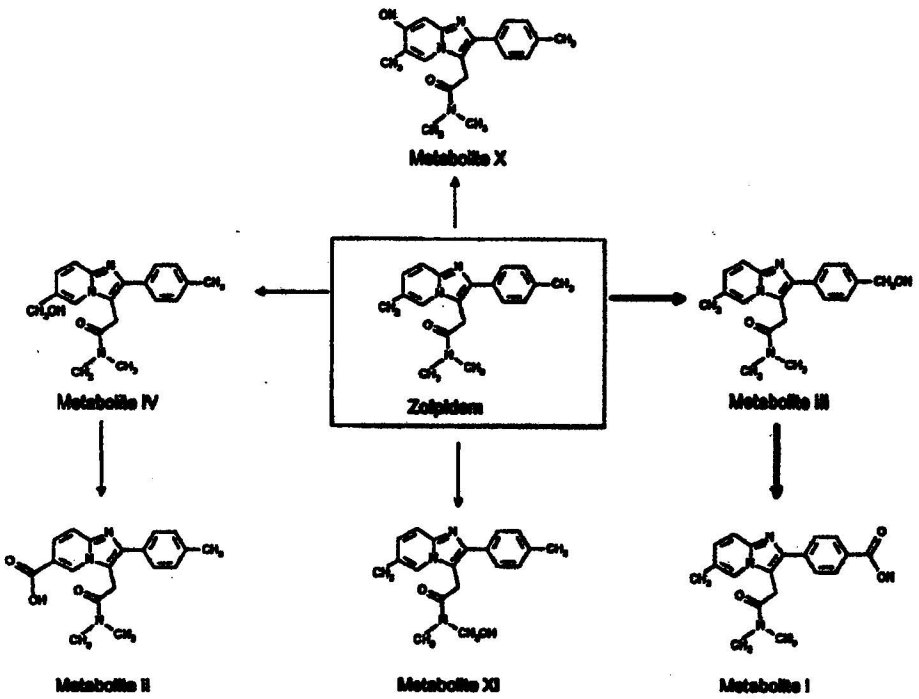


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**Table 24: Summary of Principal Pharmacokinetic Parameters (Mean [SD]) for Parent Drug and Metabolites in Subjects Treated with Zolpidem LS and Ambien Tablets**

| PK Parameter | Zolpidem LS 5 mg (N = 12) | Ambien Tablet 5 mg (N = 12) | Zolpidem LS 10 mg (N = 12) | Ambien Tablet 10 mg (N = 12) |
|---|---|---|---|---|
| **Zolpidem** | | | | |
| $C_{max}$ (ng/mL) | 114.45 (42.070) | 111.36 (31.874) | 204.24 (76.685) | 191.67 (34.538) |
| $AUC_{0-T}$ (ng•hr/mL) | 391.03 (157.130) | 420.25 (134.448) | 740.10 (304.247) | 691.68 (280.087) |
| $AUC_{0-\infty}$ (ng•hr/mL) | 415.28 (170.289) | 460.02 (159.417) | 806.00 (344.714) | 759.81 (347.104) |
| $t_{1/2}$ (min) | 158.49 (24.629) | 180.25 (48.385) | 174.58 (44.958) | 170.14 (63.032) |
| **Metabolite I** | | | | |
| $C_{max}$ (ng/mL) | 134.85 (38.839) | 145.37 (51.969) | 221.09 (67.946) | 288.38 (81.434) |
| $AUC_{0-T}$ (ng•hr/mL) | 729.85 (275.530) | 744.06 (191.676) | 1302.95 (453.233) | 1486.62 (443.209) |
| $AUC_{0-\infty}$ (ng•hr/mL) | 880.67 (407.425) | 917.80 (282.606) | 1630.33 (717.731) | 1795.83 (638.768) |
| Metabolite Ratio (MI/P) | 2.33 (0.956) | 2.24 (0.938) | 2.21 (0.873) | 2.95 (1.856) |
| $t_{1/2}$ (min) | 250.08 (82.336) | 286.21 (120.686) | 276.77 (116.165) | 266.35 (106.934) |
| **Metabolite II** | | | | |
| $C_{max}$ (ng/mL) | 0.73 (0.238) | 0.75 (0.322) | 1.28 (0.632) | 1.66 (0.741) |
| $AUC_{0-T}$ (ng•hr/mL) | 3.36 (1.682) | 3.55 (1.278) | 6.93 (3.161) | 8.08 (2.935 ) |
| $AUC_{0-\infty}$ (ng•hr/mL) | 3.84 (2.408) | 4.34 (2.350) | 8.92 (4.862) | 10.26 (4.331) |
| Metabolite Ratio (MII/P) | 0.009 (0.0058) | 0.010 (0.0049) | 0.011 (0.0056) | 0.015 (0.0061) |
| $t_{1/2}$ (min) | 259.42 (91.326) | 346.96 (176.584) | 349.75 (172.238) | 318.19 (154.156) |
| **Metabolite III** | | | | |
| $C_{max}$ (ng/mL) | 0.89 (0.347) | 0.92 (0.624) | 1.58 (1.013) | 1.92 (0.786) |
| $AUC_{0-T}$ (ng•hr/mL) | 1.19 (0.713) | 1.27 (0.918) | 2.97 (1.776) | 3.35 (1.383) |
| $AUC_{0-\infty}$ (ng•hr/mL) | 1.19 (0.713) | 1.27 (0.918) | 2.97 (1.776) | 3.35 (1.383) |
| Metabolite Ratio (MIII/P) | 0.003 (0.0018) | 0.003 (0.0023) | 0.004 (0.0018) | 0.006 (0.0037) |
| $t_{1/2}$ (min) | 86.13 (31.217) | 85.06 (33.413) | 131.73 (90.652) | 120.72 (68.691) |
| **Metabolite IV** | | | | |
| $C_{max}$ (ng/mL) | 1.61 (0.448) | 1.87 (0.557) | 3.11 (1.238) | 3.596 (0.965) |
| $AUC_{0-T}$ (ng•hr/mL) | 10.555 (3.229) | 12.09 (2.798) | 20.55 (7.023) | 21.64 (5.942) |
| $AUC_{0-\infty}$ (ng•hr/mL) | 13.41 (4.419) | 15.77 (4.230) | 26.45 (9.449) | 27.39 (7.832) |
| Metabolite Ratio (MIV/P) | 0.034 (0.0113) | 0.036 (0.0095) | 0.035 (0.0115) | 0.041 (0.0127) |
| $t_{1/2}$ (min) | 304.08 (75.078) | 324.54 (97.017) | 309.80 (93.329) | 303.58 (124.947) |
| Cross reference: Table 10.1, Table 10.2 | | | | |

**Conclusions:** On the basis of comparisons of zolpidem LS and Ambien tablets, no significant differences in drug metabolism were observed. Although there was significant variability among individual subjects, the relative metabolic fate did not vary with the dosage form to any significant degree. No new metabolites were discovered that were related to the oral spray route of administration relative to the oral tablets, evident from no extra chromatogram peaks seen for zolpidem LS compared with Ambien tablets for any of the plasma samples. Metabolites X and XI, which had been previously reported in human metabolic trials using $^{14}$C-zolpidem as minor (<10%) metabolites, were observed in blood samples after zolpidem LS or Ambien tablet dosing but were not quantified due to lack of reference standard.

## B OCP Filing Memo

**Office of Clinical Pharmacology and Biopharmaceutics**

**V.NEW DRUG APPLICATION FILING AND REVIEW FORM**

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| NDA Number | 22196 | Brand Name | ZolpiMist™ |
| OCPB Division (I, II, III) | DCP-1 | Generic Name | Zolpidem Tartrate |
| Medical Division | HFD-120 | Drug Class | Imidazole Pyridine Sedative/Hypnotic |
| OCPB Reviewer | Jagan Mohan Parepally | Indication(s) | Treatment of Insomnia |
| OCPB Team Leader | Ramana Uppoor | Dosage Form | Oral Spray |
| Date of Submission | 11/20/2007 | Dosing Regimen | 10 mg Before Bedtime |
| Estimated Due Date of OCPB Review | 8/20/2008 | Route of Administration | Oral |
| PDUFA Due Date | 9/21/2008 | Sponsor | NovaDel Pharma Inc. |
| 1.2.1.1 Division Due Date | 8/31/2008 | Priority Classification | S |

**Clin. Pharm. and Biopharm. Information**

Summary: This is a 505(b)(2) NDA to support the marketing approval of ZolpiMist™ (Zolpidem tartrate) oral spray.
Zolpimist is an oral spray formulation (1 actuation = 5 mg) of zolpidem tartrate currently marketed under trade name of Ambien in the form of tablets. The pharmaceutical development of ZolpiMist was designed to show bioequivalence between this new dosage form of zolpidem tartrate and marketed Ambien in terms of Cmax and AUC. A definitive pharmacokinetic study of ZolpiMist, 5- and 10-mg doses, in young (18–45 years of age) healthy subjects was conducted to show that ZolpiMist is bioequivalent to the reference listed drug, Ambien, at the 10-mg strength. A pharmacokinetic study of 5-mg ZolpiMist in elderly (≥65 years of age) subjects was also conducted to show that it is bioequivalent to 5-mg Ambien in this subject population.

This submission includes bioavailability data from 4 completed studies including 2 pilot studies and 2 definitive studies (one of the pilot BE study did not show bioequivalence). A summary table of clinical pharmacology studies is included in the Appendix. Three out of four studies showed bioequivalence of new formulation to the reference listed drug. Also, assessment of pharmacokinetic profile for the 5-mg dose in the elderly population (Study NVD-ZOLP-PHI-004) and evaluation of the effect of the route of administration on the human metabolite pattern of zolpidem: ZolpiMist oral spray compared to Ambien tablets (samples from 12 subjects selected randomly from Study NVD-ZOLP-PHI-003) as per pre-IND recommendations.

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments if any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |

| | | | | |
|---|---|---|---|---|
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | 2 | 2 | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | - | - | - | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | - | - | - | |
| **Plasma protein binding:** | - | - | - | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| Healthy Volunteers- | | | | |
| single dose: | X | 1 | 1 | Pilot BE Study |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | - | - | - | |
| multiple dose: | - | - | - | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | - | - | - | |
| fasting / non-fasting multiple dose: | - | - | - | |
| **Drug-drug interaction studies -** | | | | |
| in-vivo effects on primary drug: | - | - | - | |
| in-vivo effects of primary drug: | - | - | - | |
| in-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | - | - | - | |
| gender: | - | - | - | |
| pediatrics: | - | - | - | |
| geriatrics: | | | | |
| renal impairment: | - | - | - | |
| hepatic impairment: | - | - | - | |
| **PD:** | | | | |
| Phase 2: | - | - | - | |
| Phase 3: | - | - | - | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | - | - | - | |
| Phase 3 clinical trial: | - | - | - | |
| **Population Analyses -** | | | | |
| Data rich: | - | - | - | |
| Data sparse: | - | - | - | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | - | - | - | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | X | 3 | 3 | Studies also include<br>1) Effect of route of administration on metabolites<br>2) Food-drug interaction<br>3) Evaluation of PK profile in geriatric population |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X | | | |
| **Dissolution:** | - | - | - | |
| **(IVIVC):** | | | | |
| **Bio-waiver request based on BCS** | - | - | - | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | - | - | - | |
| **Chronopharmacokinetics** | - | - | - | |

| | | | | |
|---|---|---|---|---|
| **Pediatric development plan** | - | - | - | |
| **Literature References** | X | | | **64 articles referred** |
| **Total Number of Studies** | | **6** | **6** | |
| **Filability and QBR comments** | | | | |
| | **"X" if yes** | **Comments** | | |
| **Application filable?** | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? | | |
| **Comments sent to firm?** | X | 1. Please identify the parameter datasets for each study. In the electronic datasets, the columns should be given a meaningful name.<br>2. **"Define" file should clearly** indicate the meaning of each variable. Only using the results of SAS content procedure is not adequate. For example the meaning of the variables TS1-TS16.<br>3. A column should be added in the "define" file to clearly explain the meaning of the variables including the unit if applicable and how the values were obtained. For **example, variable "TRT" should be explained as "Study treatment, 1=study drug, 2=reference drug…"** | | |
| **QBR questions (key issues to be considered)** | | | | |
| **Other comments or information not included above** | **Request for DSI inspection: Pivotal bioequivalence Study NVD-ZOLP-PHI-003 and Study NVD-ZOLP-PHI-004**<br>**Clinical Research Organization (CRO):**<br>[redacted]<br>**Analytical Laboratory:**<br>[redacted] | | | |
| **Primary reviewer Signature and Date** | | | | |
| **Secondary reviewer Signature and Date** | | | | |

b(4)

**CC: NDA 22196 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Ramana Uppoor, Mehul Mehta)**

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| Table 5.2-1. Listing of NovaDel-Sponsored ZolpiMist Pharmacokinetic Clinical Studies | | | | | | |
|---|---|---|---|---|---|---|
| **Type of Study** | **Study Identifier and Location of Study Report** | **Objectives of the Study** | **Study Design and Type of Control** | **Dosing Regimen, Test Product, Route of Administration, and Duration of Treatment** | **Healthy Subjects No. of Subjects Enrolled** | **Study Status Type of Report** |
| PK Study | *NVD-ZOLP-014-04-PHI-001-US*<br>Section 5.3.3.1 | 1. Evaluate PK parameters of three doses of ZolpiMist with 10-mg Ambien in healthy adult male volunteers under fasting conditions<br>2. By design, determine dose-linearity and/or dose proportionality over ZolpiMist dose range.<br>3. Determine the maximum acceptable ZolpiMist dose and evaluate its PK profile when administered over the tongue<br>4. Provide safety and tolerability information about administrations of ZolpiMist in healthy adult male volunteers | Single-center, 4-way controlled, open-label, dose-ranging, multiple-treatment, PK study | 2.5-, 5-, and 10-mg doses of ZolpiMist (Lot L0108 Formulation 009-00) and 10-mg Ambien, oral, 4–5 weeks (4 dosing visits, 7 days [±3 days] washout period) | Healthy, adult (18–40 years of age) male volunteers<br>10 | Completed study<br>Abbreviated report[a] |
| PK Study | *NVD-ZOLP-PHI-002*<br>Section 5.3.3.1 | 1. Evaluate PK parameters of 5- and 10-mg ZolpiMist in comparison with the orally administered 5- and 10-mg Ambien in healthy male volunteers under fasting conditions<br>2. Evaluate PK parameters of 10-mg ZolpiMist after the standard high-fat breakfast<br>3. Collect safety and tolerability information about administration of ZolpiMist in healthy male volunteers<br>4. Provide assessment of PD properties of ZolpiMist as measured by the drowsiness/alertness levels associated with study drug administration | Single-center, 5-way crossover, open-label, dose-ranging, multiple-treatment, PK study | 5- and 10-mg doses of ZolpiMist (Lot 10701.001A, Formulation 027-00[b]) and 5- and 10-mg Ambien, fasting, and 10-mg ZolpiMist, fed conditions; oral, 5–8 weeks (5 dosing visits, 7 days [±3 days] washout period) | Healthy, adult (18–45 years of age) male volunteers<br>14 | Completed study<br>Full report |

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| Table 5.2-1. Listing of NovaDel-Sponsored ZolpiMist Pharmacokinetic Clinical Studies | | | | | | |
|---|---|---|---|---|---|---|
| Type of Study | Study Identifier and Location of Study Report | Objectives of the Study | Study Design and Type of Control | Dosing Regimen, Test Product, Route of Administration, and Duration of Treatment | Healthy Subjects No. of Subjects Enrolled | Study Status Type of Report |
| PK Study | *NVD-ZOLP-PHI-005*<br>Section 5.3.3.1 | 1. Evaluate PK parameters of 5- and 10-mg ZolpiMist in comparison with the orally administered 5- and 10-mg Ambien in healthy male and female volunteers under fasting conditions<br>2. Collect safety and tolerability information about administration of ZolpiMist in healthy male and female volunteers<br>3. Provide assessment of PD properties of ZolpiMist as measured by the drowsiness/alertness levels associated with study drug administration<br>4. By design, evaluate potential gender-effect of ZolpiMist on PK parameters | Single-center, 4-way crossover, open-label, dose-ranging, multiple-treatment, randomized, PK study | 5- and 10-mg ZolpiMist (Lot AA0429, Formulation 027-01[b]) and 5- and 10-mg Ambien, fasting conditions; oral, 5–7 weeks (4 dosing visits, 7 days [±3 days] washout period) | Healthy, adult (18–45 years of age) male and female volunteers<br>48 | Completed study<br>Full report |

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**Table 5.2-1. Listing of NovaDel-Sponsored ZolpiMist Pharmacokinetic Clinical Studies**

| Type of Study | Study Identifier and Location of Study Report | Objectives of the Study | Study Design and Type of Control | Dosing Regimen, Test Product, Route of Administration, and Duration of Treatment | Healthy Subjects No. of Subjects Enrolled | Study Status Type of Report |
|---|---|---|---|---|---|---|
| PK Study | *NVD-ZOLP-PHI-004* Section 5.3.3.1 | 1. Evaluate PK parameters of 5-mg ZolpiMist in comparison with 5-mg Ambien in healthy elderly male and female volunteers under fasting conditions<br>2. By design, evaluate any potential gender-effect of ZolpiMist by comparison of key PK parameters in males vs females<br>3. Collect safety and tolerability information about administration of ZolpiMist in healthy elderly male and female volunteers<br>4. Provide assessment of PD properties of ZolpiMist as measured by the drowsiness/alertness levels associated with study drug administration | Single-center, 2-way open-label, multiple-treatment, randomized, PK study | 5-mg ZolpiMist (Lot AA0429, Formulation 027-01[b]) and 5-mg Ambien, fasting conditions; oral, 2–3 weeks, 2 single doses; 7 days [±3 days] washout period) | Elderly (≥65 years) healthy male and female volunteers 24 | Completed study Full report |

[a] = Previously submitted data in IND 071290; study tested an early pilot formulation of ZolpiMist.

[b] = The composition of the final solutions produced using Formulations 027-00, 027-01, and 027-02 (the proposed commercial formulation) is identical (see *Section 3.2.P.2.2*). These formulations will be referred to as being the same and as being equivalent to that of the proposed commercial formulation. Therefore, the final clinical/commercial formula was used in Study NVD-ZOLP-PHI-002, Study NVD-ZOLP-PHI-003, and Study NVD-ZOLP-PHI-004.

PD = Pharmacodynamic.

PK = Pharmacokinetic.

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PHARMACOLOGIST

Ramana S. Uppoor
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BIOPHARMACEUTICS

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