

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**ADDENDUM TO CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA#	22196
Generic Name:	Zolpidem Tartrate
Formulation:	Lingual Spray
Sponsor:	Novadel Pharmaceuticals, Inc.
Reviewer:	Jagan Mohan Parepally, Ph.D.
Submission Type:	Addendum to Clinical Pharmacology Review

BACKGROUND

This addendum is in response to the Division of Scientific Investigations (DSI) results. At the request of Division of Neurology Products, the Division of Scientific Investigations conducted audits of the following pivotal bioequivalence studies:

Study # NVD-ZOLP-PHI-003: Single center, 4-way cross-over, open label, dose ranging, multiple treatment pharmacokinetic study of zolpidem lingual spray compared to oral tablets in healthy male and female volunteers

Study # NVD-ZOLP-PHI-004: Single center, randomized, 2-way cross-over, open-label, multiple treatment pharmacokinetic study of zolpidem lingual spray compared to oral tablets in healthy elderly volunteers.

The clinical and analytical portions of the studies were conducted at _____ and _____, respectively. Following the inspections at _____ (7/30/08 to 8/7/08) and _____ (07/15/08 to 07/17/08), Form 483s (Inspectional Observations) were issued. The clinical and analytical audit was based on 100% audit of source data.

b(4)

DSI evaluated the Establishment Inspection Report (EIR) _____, response to the Form 483 and associated exhibits related to objectionable observations including dosing deficiencies, discrepancies in PK sampling, shipment of subject samples, use of concomitant medications, randomization etc (appendix 1) and concluded that reliability of source data generated in studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004 cannot be assured due to multiple issues concerning incomplete or contradictory documentation.

b(4)

Re-Analysis of pivotal BE study NVD-ZOLP-PHI-003:

This study was conducted in healthy adult subjects. Subjects listed in the objectionable items from the clinical and analytical facility from the study NVD-ZOLP-PHI-003 were excluded to evaluate the effect on bioequivalence of the test product compared to reference. Following table indicates subjects excluded from reanalysis of pharmacokinetic parameters, $AUC_{0-\infty}$ and C_{max} .

Study NVD-ZOLP-PHI-003

Clinical Issues

Subject #	Period	Problems	Reviewer Comments
1	4	Switched information (example: A10 to Z 10) 24 days later	Excluded from analysis
2	4	Switched information 24 days later	Excluded from analysis
4	4	Switched information 24 days later	Excluded from analysis
12	4	Switched information (A10 to Z 10) 24 days later, Vomited 45 min post dose.	Cannot be verified, Excluded
13	4	Switched information (A10 to Z 10) 24 days later	Cannot be verified, Excluded
28		Dates in CRF does not match with dosing records	Excluded from analysis
22 through 25	2	PK sampling discrepancy in records (Recorded as processing sample before actual sampling)	Excluded from analysis

Analytical Issues

Study NVD-ZOLP-PHI-003

1 through 8	4	QCs failure in runs	Excluded from analysis
9	4	Sample switching between aliquot A and B (11 Samples)	Excluded from analysis
23	3	Sample switching between aliquot A and B (11 samples)	Excluded from analysis
40	3	30 min sample. Sample switching between aliquot A and B	Excluded from analysis
41	3	30 min sample. Sample switching between aliquot A and B	Excluded from analysis
44	2	Sample switching between aliquot A and B (11 Samples)	Excluded from analysis
26		90 min sample processing record discrepancy	Excluded from analysis

Subjects excluded from the analysis are limited to specific subjects stated in the inspectional observations 3 and 4 (Form 483s). Following analysis does not take into consideration of items including all subjects in the Form 483 observations related to recording errors such as priming of spray pump, randomization of study drugs.

Original analysis included 43 subjects. Reanalysis following DSI report included 37 subjects of which 22 subjects had data for all the periods of the study.

The results of re-analysis are shown in the following table. The main comparisons are between the test (Zolpidem LS 10 mg) and reference (ambient tablet 10 mg) treatment (C vs D) is highlighted in the table below. The re-analysis shows that the test and reference are bioequivalent after excluding the subjects that had recording errors.

Re-analysis of Primary PK parameters (NVD-ZOLP-PHI-003) - Excluding Subjects

Parameter	Treatment Comparisons	Ratio	Lower 90% CI	Upper 90% CI
AUC 0-∞	A vs. D	0.953	0.832	1.069
	B vs. D	0.936	0.933	1.196
	C vs. D	1.060	0.839	1.080

C max	A vs. D	0.998	0.872	1.112
	B vs. D	1.123	0.984	1.251
	C vs. D	0.943	0.822	1.049

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

Re-Analysis of pivotal BE study NVD-ZOLP-PHI-004:

Reanalysis of data from the Study NVD-ZOLP-PHI-004 was not performed since fewer subjects had clinical and analytical issues (table below) according to DSI report. This was a study conducted in elderly subjects and was a supporting study.

Study NVD-ZOLP-PHI- 004

Subject #	Problems
19 through 23 24	Doses 3 days apart Protocol (\neq 3 days) Dosing and sample processing records discrepancy

OVERALL CONCLUSIONS

Zolpidem lingual spray was found to be bioequivalent to Ambien® tablets in pivotal study NVD-ZOLP-PHI-003 after excluding subjects from the reanalysis following division of scientific investigations report.

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

Date

Veneta Tandon, Ph.D.
Acting Team Leader
Division of Clinical Pharmacology 1

Date

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

Appendix 1: DSI Memo: Review of Establishment Inspection Report Covering NDA 22-196

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 10, 2008

FROM: Sriram Subramaniam, Ph.D.
Hyojong Kwon, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 9/12/08
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-196, ZolpiMist (Zolpidem
LS (Lingual Spray)) 5, 10mg Sponsored by NovaDel, Inc.

TO: Russell G. Katz, M.D.
Director
Division of Neurological Products (DNP)

At the request of DNP, the Division of Scientific Investigations conducted audits of the following bioequivalence studies:

Study # NVD-ZOLP-PHI-003: Single center, 4-way cross-over, open-label, dose ranging, multiple treatment pharmacokinetic study of zolpidem lingual spray compared to oral tablets in healthy male and female volunteers

Study # NVD-ZOLP-PHI-004: Single center, randomized, 2-way cross-over, open-label, multiple treatment pharmacokinetic study of zolpidem lingual spray compared to oral tablets in healthy elderly volunteers

The clinical and analytical portions of the studies were conducted at _____ and _____ respectively.

b(4)

Following the inspections at _____ (7/30-8/7/08) (Attachment 3) and _____ (07/15-17/08), Form 483s were issued. The evaluation of the objectionable items follows:

Clinical Site: _____

b(4)

Both Studies

- a. Randomization of Study Drugs cannot be assured (Form 483, Item 1).**

The study drugs that were administered were not randomized at the clinical site for these open-label studies. Instead, the study drugs were preselected by the sponsor. Therefore, lot numbers of drugs administered to the subjects cannot be confirmed. Nonetheless, the lot numbers of the unused drugs matched the information provided by the sponsor.

- b. Insufficient documentation of drug accountability (Form 483, Items 3 and 6)**

The clinic failed to retain shipping records. Contrary to the clinic's procedures, the date of drug receipt was entered retrospectively. Also, the "Drug Accountability Form" was not complete for Studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004. These forms show the total number of tablets or spray bottles dispensed for each dosing day; however, the final amount and the person who performed the inventory were not identified in Study NVD-ZOLP-PHI-003 (Exhibit 1).

- c. Failure to retain medical history charts (Item 3, Form 483)**

The clinic did not have medical charts with prior screening or participation information for the 72 subjects in Studies NVD-ZOLP-PHI-003 and -004. The clinic's procedures require maintaining medical records that include screening information, medical histories, and physical test results every time the subjects were screened, as well as a list of study numbers and dosing dates for studies the subjects completed. Therefore, in the absence of medical charts, it is not possible to confirm the continued general health and suitability of the subjects enrolled in Studies NVD-ZOLP-PHI-003 and -004.

- d. Deficiencies in Dosing (Items 1, 3 and 4, Form 483)**

There was no documentation during study conduct to support priming of the sublingual sprays used in Studies NVD-ZOLP-PHI-003 and -004. The protocols required that the sprays be primed (5 actuations) prior to dosing. There was only a post-study report for Study NVD-ZOLP-PHI-003 which stated that the sprays were primed.

In addition, the following dosing discrepancies were noted:

Study NVD-ZOLP-PHI-003

The records of treatments administered were changed weeks after dosing for several subjects in Study NVD-ZOLP-PHI-003 (Item 4, Form 483 and Exhibit 2). For example, Subject #1 on Visit 4 (2/3/07) was shown to have initially received 10 mg tablet but was changed 24 days later to 10 mg lingual spray. Similar changes were made for Subjects #2 (Visit 4), #4 (Visit 4), #12 (Visit 5) and #13 (Visit 4) (Attachment 1). Also, source records revealed that subject 12 (Visit 2, 10 mg Ambien Tablet at 0941 on 1/20/07) vomited roughly 45 minutes post-dose, however, this was not reported in the case report form (Item 3, Form 483). Therefore, there is no assurance that the subjects actually received the treatments/dose they were supposed to receive.

The person who administered the doses was not delegated to perform dosing. Instead this person was responsible only for safety assessment and evaluation of adverse events, and handling and shipping of study-specific lab specimens (Item 3, Form 483,). Also, this person was not listed on the "Staff Initials Log" which reflects all staff involved in the study.

Also, the dates of dosing reported in the CRF for subject 28 in Study NVD-ZOLP-PHI-003 do not correspond to source records. Source document states that dosing dates as 1/21, 1/28, 2/4 and 2/11, while CRF lists the dates as 1/20, 1/28, 2/3 and 2/10 (Item 3, Form 483).

Study NVD-ZOLP-PHI-004

The clinic had no documentation of water consumption following dosing in Study NVD-ZOLP-PHI-004. The water restriction requirement for the study was contradictory: while protocol prohibited water consumption for at least 2 hours after dosing, "Dosing Instructions" allowed water access after 1 hour post-dose blood draw (Item 1, Form 483).

Subjects #19 -23 were dosed three days apart, although the protocol stated that dosing visits would be 7 ± 3 days apart, and the informed consent stated that "dosing visits are separated by no less than 7 days". Also, contrary to the protocol requirement, the final visit for Subject 24 was 3 days after dosing (Item 1, Form 483).

e. Discrepancies in PK sampling

For Study NVD-ZOLP-PHI-004, with the exception of the first 11 subjects, there were no records to document use/removal of catheters. The protocol and informed consent stated that all blood samples would be collected by indwelling catheter. Further, the source records showed multiple notations of late draws due to difficulty in venipuncture (Item 2, Form 483).

Also, the inspection found several discrepancies between pharmacokinetic (PK) sample collection, and handling and storage of plasma samples (Item 3, Form 483). For example in Study NVD-ZOLP-PHI-003, the 5 minute PK blood samples for subjects 22 through 25 were collected at 9:50, 9:55, 10:00 and 10:05 on 1/20/07 (Visit 2) respectively, and for Subject 26 was not scheduled to be collected until 10:10. However, the sample processing records show that the PK samples for Subjects 20-26 were stored in the freezer at 9:57, although the samples needed to be centrifuged for 10 minutes prior to storage. Also, the sample processing record for Subject 2 indicates processing of predose sample on 1/21/07 although the subject was dosed a day earlier. In contrast, pre-dose through 6 hour PK samples for Subject 24 in Study NVD-ZOLP-PHI-004 were processed on 3/19/07 while dosing records indicate that the subject was dosed the following day. Please refer to the Form 483 for more examples (Attachment 3).

f. Inconsistencies in Use of Concomitant Medications (Items 1 and 3, Form 483)

The source documents provide contradictory information for concomitant drug use. For example, the start and stop times reported in the study report for use of antihypertensives for the following subjects in Study NVD-ZOLP-PHI-004 cannot be corroborated with the source documents: Subjects #4 (atenolol), #17 (HCTZ), #19 (HCTZ), #21 (quinapril) and #24 (ramipril, timolol) (Item 3, Form 483). Although the report states that Subjects #4 discontinued their medications two weeks prior to dosing, there is no clear source documentation of when subject 4 discontinued the medications. Similarly, the start and stop dates of Acupril for Subject 21 are contradictory: The concomitant medication chart indicates start and stop times as 0730 on 3/16/07, whereas the CRF lists Acupril use between 3/16/07 and 4/2/07. Also, contrary to the sponsor's statement that Subject 19 received their medications during the study, the source documents show that the subject was taking HCTZ from 2004

and continuing. (The findings are detailed in Items 1 and 3, Form 483.)

In addition, source records provide contradictory information of concomitant drug use in Studies NVD-ZOLP-PHI-003 and -004. For example, source document for subject 6 in Study NVD-ZOLP-PHI-003 indicate use of Nyquil 25 during Visit 5 (2/10/07), however, sign-in sheet for that visit denies possession of medicines. Similarly, the concomitant drug use for Subject 24 cannot be assured. (Further examples are listed in Items 1 and 3, Form 483.)

The protocol for Study NVD-ZOLP-PHI-004 required sponsor's approval prior to first dosing for subjects taking any concomitant medications. However, study records provide conflicting information of sponsor's approval for several subjects in Study NVD-ZOLP-PHI-004 who were taking antihypertensive drugs. (Item 1, Form 483 details the contradictions.) Also, there was no record to support sponsor's approval of subject 24, who was taking Timolol.

g. Discrepancies in Shipment of subject samples (Form 483, Item 3)

Correspondence files revealed multiple discrepancies between the clinic's shipment forms and the samples actually received by the analytical site in Study NVD-ZOLP-PHI-003. The records of shipment were not complete: Some of the forms were contradictory, and there were several communications from the analytical site and the sponsor concerning missing (or extra) samples for almost every shipment. The analytical site either received samples for subjects not listed in the shipping form or did not receive samples for subjects listed on the forms. For example, the Summary of Shipment form dated 1/22/07 states that it includes a total of 40 subjects (total of 638 samples) in Study NVD-ZOLP-PHI-003, but does not list samples for Subjects #17, #18 and #32. Also, there was no shipment record for set A Period 1 samples for Subject 41 in Study NVD-ZOLP-PHI-003.

h. IRB approval and Informed Consent (Item 2, Form 483)

Correspondence records for Study NVD-ZOLP-PHI-003 revealed that the sponsor added additional criteria for subject selection based on race and age, as they were concerned with the high percentage of randomized subjects who were African American (19 of the first 27 screened). However, this change was not approved by the IRB.

The screening consent signed by each female subject stated that screening tests would include a 'urine pregnancy test if applicable,' however, the study specific consent signed by each subject does not include any mention of pregnancy testing. Nonetheless, pregnancy testing was conducted for the 18 female subjects in Study NVD-ZOLP-PHI-004 at screening, at each dosing period check in and at the final visit.

i. Failure to retain sufficient reserve samples (Form 483, Item 5).

The sponsor did not send sufficient study drugs for retention of reserve samples. The sponsor sent only 80 and 36 prepackaged, pre-labeled, pre-numbered kits for Studies NVD-ZOLP-PHI-003 and -004, respectively. The total quantities remaining after the two studies were less than required to conduct 5 times release testing. For example, only 47, 34 and 80 units of 5 mg tablets, 10 mg tablets and sublingual spray bottles were retained. In contrast, the 5X quantity of unit doses that needed to be retained was greater than 350.

Analytical Site: _____

b(4)

**j. Analytical observations for Study NVD-ZOLP-PHI-003:
Analytical runs were accepted when more than 50% of the High Quality Control Samples (QCs) failed.**

Specifically, analytical runs that measured zolpidem concentrations in phase 4 samples for Subjects #1 to #8 (dated February 20, 2007), and metabolite-1 and metabolite-2 concentrations for Subjects #22 and #23 (dated June 14, 2007) were accepted although two of the three (67%) high QCs failed in each run.

k. Data were reported from sample assay when there was question about identity and integrity of samples.

In study NVD-ZOLP-PHI-003 the concentration data for the 30 minute sample for Subjects #40 and #41 in Period III were switched (Table 9 of the final report for Set-A, 'FL07-NVD-TR115R2'). The reason for switching of the above data cannot be confirmed as the documentation at the clinical site was not definitive about the sample switching (See Attachment 1, FL07-NVD-RT361).

Also, _____ observed discrepancies between the set-A and set-B data in 11 samples from Subjects #9, #23 and #44 (see Table 1 in Attachment 2). _____ suspected the discrepancies were due to switching of the aforementioned samples from Set A during analyses. However, sample switching could not be confirmed by _____ (See Attachment 2). Since, Set A and Set B concentrations do not match and sample switching cannot be confirmed, the accuracy of concentrations for the 11 samples from Subjects #9, #23 and #44 cannot be assured.

b(4)

Conclusions:

Based on the above findings, we recommend the following:

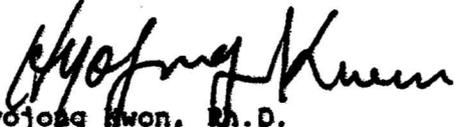
Studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004

- The multiple deficiencies in clinical conduct, and the incomplete or contradictory documentation (Items a to i), fail to assure confidence in the clinical conduct of Studies NVD-ZOLP-PHI-003 and NVD-ZOLP-PHI-004.

Study NVD-ZOLP-PHI-003

- The accuracy of the zolpidem concentrations for Subjects #1 to #8 (Period 4), and metabolite-1 and metabolite-2 concentrations for Subjects #22 and #23 cannot be assured.
- The accuracy of zolpidem concentrations for the 11 samples for Subjects #9, #23 and #44 (see Table 1, Attachment 2) cannot be assured.
- The accuracy of the zolpidem concentrations for subject #40 and #41 at 30-minutes in Period III cannot be assured.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

 9/10/08
Hyojoag Won, Ph.D.


Sriram Subramaniam, Ph.D.

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Final Classifications:

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b(4)

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HFD-48/O/Kwon/Subramaniam/CF
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